CB 20/82/01

NCI/ICRDB/CB20 82/01

PB82-932301

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CANCERGRAM

ANTITUMOR AND ANTIVIRAL AGENTS

Experimental Therapeutics, Toxicology, Pharmacology

SERIES CB20 No. 82/01

JANUARY, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

ANTITUMOR AGENT EFFICACY IN VIVO

1. EXPERIMENTAL STUDY ON CHEMOTHERAPY OF URINARY BLADDER CANCER IN RATS.

Kamiryo Y, Sakatoku J, Wang CY, Bryan GT
Dept. Urology, Yamaguchi Univ. Sch. Medicine, Ube, Yamaguchi Prefecture 755, Japan
Nippon Gan Chiryo Gakkai Shi; 16(2):209-219 1981

Antitumor effects of thiotepa (T), adriamycin, methotrexate, cyclophosphamide (CP), phosphoramide mustard (PM), and nornitrogen mustard (NM) were investigated in Fisher 344 female rats that were given transplants of Chapman R4909 rat urinary bladder cancer cells. Initially, the rats were given injections of the rat cancer cells in three different concentrations, and the rats were sacrificed at wk 2, 4, and 6 after transplantation. All of the rats developed urinary bladder tumors. Next, rats were given cancer cell transplants, and for 4 days following the transplantation, each rat was given a particular dose of a particular drug intravesicularly. These rats were sacrificed 6 wk later, and the antitumor effects of the drugs were assessed. Tumor occurrence was completely prevented by 0.3 mg/kg body wt of T, 35.0 or 8.8 mg/kg of CP, and 50.0, 12.5, or 5.0 mg/kg of the PM or NM. Rats that died prior to wk 6 usually died within 1 wk of the intravesicular infusion of the drugs and died due to toxic effects of the drug on the urinary bladder mucosa. This animal model was considered to be an appropriate method to study recurrence-preventive effects of antitumor drugs on urinary bladder cancer. (66 Refs) (In JPN)

2. TILORONE-MEDIATED PROTECTION AGAINST MURINE B16 MELANOMA.

Turner EV, Wallace JH
(c/o Wallace) Dept. Microbiology and Immunology, Univ. Louisville Health Sciences Center, Louisville, KY, 40292
Proc Soc Exp Biol Med; 167(4):536-541 1981

The effects of tilorone hydrochloride (THC) on the growth of B16 murine melanoma was investigated. Mice were injected with 10(4) B16 cells and treated ip with 0.25 ml saline with or without 1 mg THC daily following tumor injection. Mice were observed for 90 days and tumor wt was obtained on day of death. THC-treated mice showed lower tumor incidence, increased survival time and lower av tumor wt than controls. All control groups had tumors and all died. During the period of observation, 40% of THC-treated mice did not develop tumors. In an in vitro study with B16 and C57Bl/6 fibroblasts, THC showed no selective toxicity for the B16 cells. Cell growth in these two cell types was not inhibited at THC concentrations from 0.5-0.05 ug/ml. A dose-response growth inhibition of THC-treated peritoneal exudate cells for B16 cells was observed. Adherent peritoneal exudate cells from THC-treated mice and products from such cells inhibited B16 growth in a dose-dependent manner. These results demonstrate that both cytotoxic effects and enhanced macrophage functions appear to have contributed to the reduced B16 melanoma growth observed in THC-treated animals. (26 Refs)

3. ANTITUMOR ACTIVITY OF 3'-5'-DIESTERS OF 5-FLUORO-2'-DEOXYURIDINE AGAINST MURINE LEUKEMIA L1210 CELLS.

Kanzawa F, Hoshi A, Kuretani K, Saneyoshi M, Kawaguchi T
Pharmacology Div., Natl. Cancer Center Res. Inst., 5-1-1, Tsukiji, Chuo-ku, Tokyo 104, Japan
Cancer Chemother Pharmacol; 6(1):19-23 1981

The antitumor activity of 3',5'-diesters of 5-fluoro-2'-deoxyuridine (FUdR), which are depot forms of FUdR, was examined. The relation between the antitumor activity of these diesters and the kinetic behavior of the compound after dosing was studied. An increase in survival time with increasing diester dose was noted in male BDF1 leukemia L1210-bearing mice until the dose reached 100mg/kg/day. The max increase in lifespan over controls (ILS) was 54%. The value of ILS30 (the dose showing 30% increase in lifespan), determined graphically by the dose-response curve, was 50 mg/kg/day and its therapeutic ratio was 2.0. Esters of FUdR with aliphatic acid or shorter chain length did not appear to be as active as unesterified FUdR. The ILS30 values of 3',5'-diesters of FUdR with acetyl, propionyl, and butyryl were 100, 140, and 190 mg/kg/day, respectively. However, the antitumor activity of the ester with an aliphatic acid of intermediate chain length (hexanoyl) was approx 20x greater than that of FUdR. The most active agent in the aliphatic ester series was the longer-chain ester (palmitoyl). Esters of FUdR derived from other than aliphatic acids, aryl esters, were also markedly active against L1210 cells. The plasma levels of the active metabolites of FUdR were determined and confirmed that the maintenance of a high level of FUdR over a considerable period produces an enhanced antitumor effect. The results indicated that the cytotoxicity of diesters of FUdR is correlated with the duration of a high plasma level of FUdR. (30 Refs)

4. STUDIES ON THE ANTITUMOR EFFECT OF ANAEROBIC BACTERIA. I. THE EFFECT OF FUSOBACTERIUM NUCLEATUM ON EHRLICH'S ASCITES TUMOR (MEETING ABSTRACT).

Tamai K
Dept. Oral Surgery, Sch. Medicine, Kanazawa Univ., Kanazawa-shi, Ishikawa Pref. 920, Japan
Nippon Saikingaku Zasshi; 36(1):330 1981

The antitumor effects of culture supernatants, heat-killed (100 C, 20 min) bacterial cells, and sonicated supernatants of cultured bacteria of Fusobacterium nucleatum strain KO-31, isolated from human dental calculus, in ICR mice inoculated with Ehrlich's ascites tumor (ES) cells were examined. While all of the control mice inoculated ip with 3.7 x 10(6) ES cells died from their tumors between days 13 and 20, 17 of 20 mice treated with the culture supernatants survived 60 days without showing ascites at autopsy. No antitumor effects were observed with the killed bacterial cells or the sonicated supernatants. (no Refs) (In JPN)

5. ANTITUMOR EFFECT OF DICYCLOHEXYLAMMONIUM SULFATE, A POTENT INHIBITOR OF SPERMIDINE SYNTHASE.

Hibasami H, Ito H
Dept. Biochemistry, Mie Univ. Sch. Medicine, Edobashi 2-174, Tsu 514, Japan
Gan; 72(4):512-516 1981

The antitumor effect of dicyclohexylammonium sulfate (DCHA), a potent inhibitor of spermidine synthase, was tested on mice inoculated with Ehrlich ascites carcinoma, Ehrlich solid carcinoma and solid sarcoma-180. DCHA prolonged the survival time of mice bearing Ehrlich ascites carcinoma at doses of 50-100 mg/kg/day x 5. For Ehrlich solid carcinoma and solid sarcoma-180 the tumor growth was suppressed significantly at doses of 2-50 mg/kg/day x 10. The spermidine concentration of the tumor cells was lowered, while the spermine concentration hardly changed. The depletion of spermidine in the tumor cells might be a cause of the suppression of tumor growth. (Author abstract) (24 Refs)

6. MERCURY-INDUCED NECROSIS OF MURINE RENAL CELL CARCINOMA.

Herr HW, Kleinert EL, Whitmore WF
Urology Section, Sloan-Kettering Inst., Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
J Surg Oncol; 18(1):95-99 1981

Administration of the nephrotoxic agent, bichloride of mercury (Hgl2), to BALB/c mice bearing subcapsular renal tumor transplants induced early preferential necrosis of the tumor cells compared with mercury-treated normal kidney tubular cells and untreated control tumors. The principle is established that a selective proximal tubular poison is also toxic for a tumor of the same cellular origin. (Author abstract) (3 Refs)

7. EVALUATION OF MEGADOSE VITAMIN THERAPY IN AN EXPERIMENTAL BRAIN TUMOR.

Newell SD, Kapp J, Romfh JH
(c/o Kapp) Dept. Neurosurgery, Univ. Mississippi Sch. Medicine, 2500 N. State St., Jackson, MS, 39216
Surg Neurol; 16(2):161-164 1981

A mixture of vitamins C and B12 in high dosage, which has been reported to eradicate ascites tumors in rats, was tested for its antineoplastic effect against the L9 glioma in Fisher CDF strain rats. No difference in survival time between animals receiving the vitamin mixture and controls could be demonstrated. Possible reasons for the different response to therapy in the two experimental tumor systems are discussed. (Author abstract) (11 Refs)

8. ANTITUMOR ACTIVITY OF TUFTSIN ON MURINE MELANOMA IN VIVO.

Noyes RD, Babcock GF, Nishioka K
(c/o Babock) Dept. Surgery/Surgical Res. Lab., Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer Treat Rep; 65(7/8):673-675 1981

The effect of tuftsin on malignant melanoma was studied in vivo using a murine model system. It was found that tuftsin was capable of significantly reducing the number of tumor colonies appearing in the lungs of mice following iv administration of tumor cells. Although only a limited number of concentrations of tuftsin were used in our preliminary studies, it appears that tuftsin possesses antitumor activity over a wide range of doses. (Author abstract) (21 Refs)

ANTITUMOR AGENT EFFICACY IN VITRO

9. EFFECT OF CIS-DICHLORODIAMMINEPLATINUM(II) ON CLONED OVARIAN ADENOCARCINOMA CELLS OF THE RAT IN VITRO.

Sekiya S, Iwasawa H, Yamauchi K, Kubota K, Takamizawa H
Dept. Obstetrics and Gynecology, Chiba Univ. Sch. Medicine, 1-8-1 Inohana, Chiba 280, Japan
Gynecol Oncol; 12(1):14-22 1981

Cloned rat ovarian adenocarcinoma cells (ROT58/C3) treated for 1 hr with 0.5 ug/ml or more of cis-dichlorodiammineplatinum(II) (DDP) or adriamycin (ADM) revealed a marked decrease in survival as estimated by the colony-forming method. Compared to cloned rat uterine adenocarcinoma cells (HTP/C1), the ROT58/C3 cells were more sensitive to the cytotoxic effect of both drugs. The survival of exponentially growing ROT58/C3 cells was reduced to less than 10% by a 0.5 ug/ml dose of DDP, as compared to a 1 ug/ml dose of ADM. Extensive morphological changes such as enlargement of the nuclear and nucleolar diameters, increase in the number of nucleoli, and the appearance of coarse and opaque chromatins were observed by optical and electron microscopy at as early as 48 hr after exposure to DDP for 1 hr. In addition, accumulation of cells at the G2 phase in the cell cycle was observed by flow microfluorometry. (Author abstract) (13 Refs)

10. VITAMIN K3 (MENADIONE) INHIBITS THE GROWTH OF MAMMALIAN TUMOR CELLS IN CULTURE.

Prasad KN, Edwards-Prasad J, Sakamoto A
Dept. Radiology, Sch. Medicine, Univ. Colorado Health Sciences Center, 4200 E. 9th Ave., Denver, CO, 80262
Life Sci; 29(13):1387-1392 1981

The effects of vitamin K on the morphology and the growth of mouse neuroblastoma (P2), mouse melanoma (B-16) and rat glioma (C-6) cells in culture were studied. Vitamin K3 inhibited the growth (due to cell death and partial or complete inhibition of cell division) of all three cell types without causing any morphological differentiation. Vitamin K3 was more effective than vitamin K1. Neuroblastoma cells were more sensitive to vitamin K3 than were melanoma or glioma cells. Glioma cells did not grow in hormone-supplemented serum-free medium; however, both neuroblastoma and melanoma cells grew to a level 70-80% of that found in serum-supplemented medium. Neuroblastoma cells and melanoma cells cultured in serum-free medium exhibited a 2-3 fold higher sensitivity to vitamin K3 than those cultured in serum-supplemented medium. This suggests that serum factors attenuate the growth inhibitory effect of vitamin K3 on tumor cells in culture, probably by reducing the availability of this vitamin to the cells. Neuroblastoma cells were more sensitive to vitamin K3 than were melanoma cells even when they were treated in serum-free medium. The fact that uM concentrations of vitamin K3 inhibit the growth of tumor cells in culture suggests that this vitamin may be a potentially useful anticancer agent. (Author abstract) (11 Refs)

11. ETHANOL MUSTARD CYTOTOXICITY IN VITRO TOWARD MURINE LEUKEMIA AND BONE MARROW PROGENITOR CELLS.

Naujokaitis SA, Fisher JM, Rabinovitz M
Lab. Medicinal Chemistry and Biology, NCI, NIH, Bethesda, MD, 20205
Res Commun Chem Pathol Pharmacol; 33(2):305-318 1981

Ethanol mustard, 2-[bis(2-chloroethyl)amino]ethanol-picrate, was approx one tenth as cytotoxic as mechlorethamine toward both murine bone marrow progenitor cells and L1210 leukemia cells. Choline protected cells against nitrogen mustard cytotoxicity, but increased their sensitivity toward ethanol mustard. 2-(Di-n-butylamino)ethanol was the best protector of both bone marrow precursor cells and L1210 cells against ethanol mustard cytotoxicity. Both ethanol mustard and 2-(di-n-butylamino)ethanol showed non-competitive inhibition of choline transport. (Author abstract) (14 Refs)

12. MODE OF ACTION OF GCE: AN ACTIVE ANTICANCER PRINCIPLE ISOLATED FROM AN INDIGENOUS PLANT GYMNOSPORIA ROTHIANA LAWS.

Chapekar MS, Sahasrabudhe MB
Dept. Pathology, Arlington Hosp., George Mason Drive, Arlington, VA
Indian J Exp Biol; 19(4):333-336 1981

The mechanism of action of chloroform ether extract (GCE), obtained from the roots of the plant Gymnosporia rothiana Laws, on L-1210 and P-388 transplantable tumors from BDF1 mice was examined. The viability of P-388 cells following treatment with 1 and 10 ug GCE was reduced to 68% and 58%, respectively, after 6 hr of drug exposure. After 4 and 6 hr of exposure to 100 ug GCE, the viability of P-388 cells was reduced to 58% and 27%, respectively. The viability of L-1210 cells was reduced to 40% and 0% after 6 hr of exposure to doses of 50 and 100 ug of GCE, respectively. In vivo animal bioassay studies indicated that GCE killed 90% and 98% of the cells after 2 and 6 hr in vitro exposures, respectively, of 1 x 10(6) cells to 100 ug GCE. For 10 ug of GCE, inhibition of DNA, RNA, and protein biosynthesis was 17%, 19%, and 50%, respectively. At 80 ug GCE, inhibition of the macromolecules was about 70%. Administration of 25 ug/kg GCE/mouse to L-1210 tumor bearing mice led to max protein synthesis inhibition after 12 hr of GCE treatment, max RNA synthesis inhibition after 24 hr, and max DNA synthesis inhibition after 36 hr. (11 Refs)

13. MECHANISM OF THE EFFECT OF THE ANTICANCER ANTIBIOTIC NEOCARZINOSTATIN (NCS). VIII. SYNERGISTIC ACTION OF THE PROTEIN COMPONENT (PC) AND THE NONPROTEIN COMPONENT (NPC) (MEETING ABSTRACT).

Ebina T, Sato A, Edo K, Ishida N, Koide Y
Dept. Bacteriology, Tohoku Univ., Sch. Medicine, Sendai-shi, Miyagi Pref. 980, Japan
Nippon Saikingaku Zasshi; 36(1):232 1981

It was previously reported that neocarzinostatin (NCS) is composed of two components, PC and NPC, which differ from each other in the nature of their activity. In this study purified PC and NPC and a recombination of the two components were compared for their in vitro effects on paracrystal formation and spreading of cancer cells and on bacterial growth. Paracrystal formation by HeLa cells observed by phase-contrast microscopy and spreading of HeLa cells observed by Giemsa staining were not inhibited by single PC or NPC, and the marked inhibition of both phenomena shown by NCS was only partly restored by a mixture of PC and NPC at the same ratio as in NCS. The minimum inhibitory concentration for Sarcina lutea was 3.1 ug/ml for NCS and 12.5 ug/ml for NPC, whereas PC did not inhibit the bacterial growth even at 100 ug/ml. Since it was previously shown that in vitro cutting of DNA chains is caused by NPC, it is suggested that PC acts as a carrier of NPC for NPC to combine with the cell membrane. (no Refs) (In JPN)

14. STEROID RESPONSIVENESS OF THE HUMAN CELL LINE NHIK 3025.

Ostgaard K, Wibe E, Eik-Nes KB
Inst. Marine Biochemistry, N-7034 Trondheim-NTH, Norway
Acta Endocrinol (Kbh); 97(4):551-558 1981

The human cell line NHIK 3025, derived from a carcinoma of the uterine cervix, contains a glucocorticoid and an androgen receptor. The effect of various natural and synthetic steroid hormones and antihormones on growth rate of these cells was therefore investigated. Cells grown in Eagle's MEM with 10% fetal calf serum exhibited reduced growth when cultured with dexamethasone due to prolongation of the cell cycle. Glucocorticoid anti-inducers like progesterone had no significant effect on cell growth. Methyltrienolone (R 1881) or 5alpha-dihydrotestosterone did not affect cell proliferation. The reported shortening of the cell cycle by testosterone is probably not directly connected with activation of the androgen receptor present, but possibly dependent on metabolic conversion of testosterone to the more potent growth stimulator 4-androstene-3beta,17beta-diol. The effect of several anti-androgens was also studied. The non-steroidal anti-androgens flutamide and SCH 16483 had no significant effect on cell proliferation. It was, however, found that a number of steroid anti-androgens, including R 2956, stimulated cell growth. A significant stimulatory effect by R 2956 was seen within the first cell generation, 4-androstene-3beta,17beta-diol had to be present during 2 days, and testosterone for even longer times before a similar effect on cell growth could be obtained. (Author abstract) (24 Refs)

15. INCREASE IN CYTOTOXICITY OF CYTOSINE ARABINOSIDE AND INHIBITION OF DEGRADATION OF CYTOSINE ARABINOSIDE TRIPHOSPHATE (ARA-CTP) BY HYDROXYUREA IN HUMAN LYMPHOBLASTIC CELLS.

Abe I, Saito S, Suzuki M, Sato H
Res. Inst. Tuberculosis and Cancer, Tohoku Univ., Sendai-shi, Miyagi Pref. 980, Japan
Gan To Kagaku Ryoho; 8(2):248-255 1981

The relationship between the metabolism of cytosine arabinoside (ara-C) and the sensitivity to the drug, and the effect of hydroxyurea (HU) on this relationship were examined in human lymph oblastic cell lines, MOLT-4F, Raji, and Daudi cells. Inhibition of DNA synthesis by ara-C was marked in MOLT-4F, Raji, and Daudi, in decreasing order, in accordance with the growth inhibition and intracellular accumulation of ara-C nucleotides during 4 hr incubation. The ara-C nucleotide level was maintained by both production and degradation, but it was found that HU could increase the nucleotide level by inhibiting the degradation in Raji and Daudi, whose dephosphorylating ability was high as compared to MOLT-4F. When ara-C incorporation was examined in the presence of 0.3 mM HU, the ara-C nucleotide level accumulated after 4 hr incubation was 3x higher than that in the absence of HU in Raji and Daudi. The nucleotide level was not changed by HU in MOLT-4F, which was poor in the dephosphorylation of the nucleotides. Since about 85% of the nucleotides were identified as ara-CTP by thin-layer chromatography, the change in ara-C nucleotides should reflect the change in ara-CTP. As a result of combination therapy carried out on the basis of the above observations, a marked synergistic effect was obtained in Raji, where the tumor cell reduction was seven-fold the expected value. The effect was additive in Daudi. The combination, however, gave no advantage to MOLT-4F, suggesting that the combination is preferable when the degradation of ara-CTP was concerned with the drug sensitivity. (Author abstract) (29 Refs) (In JPN)

16. ICRF 159-INDUCED CELL-CYCLE PERTURBATION IN VITRO: ITS RELATIONSHIP TO INHIBITION OF COLONY-FORMING ABILITY.

Edgar DH, Creighton AM
Dept. Immunology, ARC Inst. Animal Physiology, Babraham, Cambridge CB2 4AT, England
Br J Cancer; 44(2):236-240 1981

The effects of single doses of ICRF 159 (Razoxane) on the cell-cycle kinetics of lines of BHK 21S cells in vitro were studied by means of flow microfluorometry (FMF). A characteristic accumulation of cells in the 4n DNA region after 6 hr in the presence of ICRF 159 was evident in cells which were sensitive to the cytotoxic effects of the agent, as judged by colony-forming assays. The subsequent accumulation of 8n cells as the major population within 24 hr indicates that this 6 hr effect is associated with the induction of tetraploidy through abnormal mitosis, rather than reflecting a G2 block of potential value in combination therapy. In ICRF 159-resistant sublines, the cell-cycle distributions were similarly affected, but only by doses of the drug high enough to reduce their surviving fraction. Somatic cell hybrids from crosses between sensitive and resistant cells demonstrated intermediate responses to ICRF 159, both in terms of cell-cycle kinetics and impairment of reproductive integrity. These data suggest a relationship between the two manifestations of the cellular action of ICRF 159, and also a possible predictive role for FMF in the assessment of response to this particular agent. (Author abstract) (14 Refs)

17. GRANULOCYTIC CHALONE (GC) EFFECT ON THE GROWTH PATTERN OF CONTINUOUS LEUKAEMIC CELL LINES.

Foa P, Maiolo AT, Lombardi L, Binda U, Polli EE
Istituto di Clinica Medica I, Univ. Milan, Milan, Italy
Cell Biol Int Rep; 5(8):761 1981

In vitro actions of the granulocytic chalone (GC) on the growth pattern of leukemic cell populations were assessed. GC was prepared by incubating peripheral ox WBC in saline (4 hr, 37 C) and purifying the conditioned medium by ultrafiltration on Amicon membranes and the fraction with a nominal mol wt = 500-10,000 dalton was further purified by Sephadex G25 filtration. 100 ug/ml GC were added every 12 hr for 48 hr to the following continuous leukemic cell lines growing in suspension culture: rat acute myeloid W25, human acute promyelocytic HL60, and human T lymphoblastic line 8402. Cell proliferation, assessed by serial count, was significantly inhibited in both the rat W25 and human HL60 cultures, but not in the human 8402 cells (respective doubling times in hr, versus untreated controls, were 21.0/15.0, 52.5/36.0, and 29.5/29.5). GC-induced inhibition of growth in W25 and HL60 cell lines was spontaneously reversible approx 18 hr after discontinuing treatment, when growth rates returned to control levels. GC in vitro was shown to exert a powerful but non-toxic, myeloid- but not species-specific, inhibitory action on leukemic cell populations. (4 Refs)

18. EFFECT OF METHYLMERCURY(II) ON THE SIZE OF HELA S3 CARCINOMA CELLS.

Gruenwedel DW
Dept. Food Science and Technology, Univ. California, Davis, CA, 95616
Virchows Arch [Cell Pathol]; 37(2):153-166 1981

HeLa S3 suspension-culture cells were exposed to methylmercury(II) of sub-lethal ([CH3Hg(II)] less than 3.2 uM) and lethal ([CH3Hg(II)] greater than or equal to 3.2 uM) concentrations for varied periods of time and their changes in vol monitored with the help of electric sensing zone instrumentation. The vol distribution of the cells was found to follow in almost all instances the logarithmic normal distribution. When deviations occurred, they were approximated as following a Gaussian distribution. Information on measures of central location such as median, mode, mean, and variance has been presented in tabulated form as a function of both organomercurial concentration in the growth medium and length of incubation. The cells were found to respond to increasing concentrations of methylmercury by at first enlarging their vol and then, particularly at high toxicant levels and after longer periods of incubation, by decreasing it. While the vol increase, reaching almost twice the vol of control cells, was generally accompanied by a spreading of the size distribution, indicating the presence of many differently-sized cells, the vol decrease led in all instances to a considerable narrowing of the distribution. The vol decreased by a factor of three-to-four below that of control cells. Scanning electron microscopy (SEM) of HeLa S3 cells at the toxicant levels listed above, but limited to a 12 hr incubation period, supplemented the vol distribution measurements. As revealed by SEM, cells that are characterized by a wide size distribution possess a multitude of shapes and surface features while cells with narrow distributions are homogeneous in appearance. It was found that cell sizing, utilizing electric sensing zone instrumentation, represents a technique that is extremely sensitive to minor changes in cell vol and vol distribution and that it is thus uniquely suited to detect cellular injury at early stages of pathological conditions brought about by organic mercury compounds. (Author abstract) (17 Refs)

19. CYTOCHALASIN B RESISTANT MUTANTS OF FRIEND ERYTHROLEUKAEMIA CELLS.

Neill R, McMenamin M, Hickey I
Sub-Dept. Genetics, Queen's Univ. Belfast, Belfast, Northern Ireland
Cell Biol Int Rep; 5(8):766 1981

Survival of clone 707 Friend Erythroleukemia (FEL) cells in the presence of 2.0 ug/ml cytochalasin B (CB) was monitored for 11 days. By day 3 survival frequency had been reduced to 1.5 x 10(-3) and remained at this level until day 7, after which it rose to 1.4 x 10(-2) by day 11. Only clones isolated after day 7 showed appreciable resistance to CB; in five of these cell lines generation time was approx double that for CB-free controls (mean ranges of doubling times 19.8-29.0 versus 10.9-12.6 hr). Cloning efficiency of all five mutant clones was reduced (16.7-38.5 versus 56.0-76.0 in controls). Growth could be observed in up to 8.0 ug/ml CB, while in wildtype FEL cells growth was totally inhibited at 1.4 ug/ml CB. After 40 hr in the presence of CB, a low level of clonal multinucleation was observed: 83.2-89.6% of cells were mononucleate (1.7% in wildtype). In the absence of CB, resistance was retained: re-exposure for 7 days did not reduce subsequent cloning efficiency in CB-free medium. Little difference in 3H-CB cellular binding or karyotype was observed between wildtype cells and the five mutant clones. No increased resistance to colchicine could be found in the mutant cell lines. (2 Refs)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

20. A NEW APPROACH TO CANCER CHEMOTHERAPY: SELECTIVE ENHANCEMENT OF TUMOR BLOOD FLOW WITH ANGIOTENSIN II.

Suzuki M, Hori K, Abe I, Saito S, Sato H
Dept. Oncology, Res. Inst. for Tuberculosis and Cancer, Tohoku Univ., 4-1 Seiryomachi, Sendai 980, Japan
JNCI; 67(3):663-669 1981

Elevation of the mean arterial blood pressure to approx 150 mm Hg by infusion of angiotensin II resulted in an approx 5.7-fold selective increase in blood flow in tumor tissue without increasing blood flow in normal tissue. This finding of no autoregulation of blood flow in tumor tissue was made in an experiment on inbred DONRYU rats with sc transplanted AH109A solid tumors (Yoshida ascites hepatoma). Changes in tissue blood flow were measured by a thermo-electrical method. In another experiment in which DONRYU rats with sc transplanted AH272 solid tumors were used, the chemotherapeutic effect of mitomycin C on main tumors and lymph node metastatic foci was markedly enhanced in rats with angiotensin-induced hypertension, as compared to its effect in rats without angiotensin-induced hypertension. Thus a new approach to cancer chemotherapy has been demonstrated in which the delivery to tumor tissue of systemically administered anticancer drugs can be selectively enhanced. (Author abstract) (30 Refs)

21. RADIATION-SENSITIZING EFFECT OF RUBOMYCIN AND ITS COMPLEX WITH DNA.

Riabchenko NI, Smoryzanova OA, Dedenkov AN
Res. Inst. Medical Radiology, Obninsk, USSR
Med Radiol (Mosk); 26(7):46-50 1981

The radiosensitizing effect of antitumor antibiotic rubomycin (RM) and its complex with DNA was studied in C57BL mice with ip transplanted Ehrlich ascites carcinoma (EAC). On day 4 after EAC transplantation, animals were subjected to a whole-body gamma irradiation (100-500 rads); 1 hr prior to irradiation, mice were inoculated ip with RM or RM-DNA at 2, 5 and 7 mg/kg. Estimation of the specific rates of tumor cell proliferation showed that RM-DNA administration prior to irradiation provided a more effective inhibition of tumor growth than free RM or irradiation alone. (13 Refs) (In RUS)

22. KINETICALLY DIRECTED COMBINATION THERAPY WITH ADRIAMYCIN AND X-IRRADIATION IN A MAMMARY TUMOR MODEL.

Braunschweiger PG, Schenken LL, Schiffer LM
Cancer Res. Lab., Allegheny Singer Res. Corporation, Allegheny General Hosp., Pittsburgh, PA, 15212
Int J Radiat Oncol Biol Phys; 7(6):747-753 1981

Cell kinetic perturbations induced by 200 rad x-irradiation (X) and 1 mg/kg ip adriamycin (ADR) separately or in combination were studied in T1699 mouse mammary tumors transplanted into male DBA/2J mice. The mitotic and thymidine labeling indices were determined in vitro at various intervals after separate or combined treatment; treatment efficacy was evaluated by tumor regrowth measurement in tumor-breeding mice. Kinetic results indicated that ADR and X each induced a 9-10 hr G2 block in cell progression. ADR and X given together increased S-phase transit time and G2 progression delay. Optimum sequences for subsequent ADR + X fractions were derived from the recovery kinetics after combined treatment: treatment schedules of up to four fractions were designed and assessed by the regrowth delay measurements. Greatest regrowth delay was seen in mice treated with ADR + X at 0, 15, 48, and 81 hr. Median survival for this group was 45 days. Thus, antitumor activity of ADR + X was enhanced by an inter-fraction interval that minimized proliferative recovery between fractions. (35 Refs)

23. MODIFYING EFFECT OF COBALAMINES ON TUMOR GROWTH.

Miasishcheva NV, Golenko OD, Arsenian FG, Gerasimova GK, Vares IuV
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (7):24-31 1981

The ability of methylcobalamine (MCA) antagonists to enhance the therapeutic efficacy of methotrexate (MTX) was studied in transplantable solid murine tumor systems (mammary gland adenocarcinoma Ca 755, carcinoma cervix uteri CC 5, adenocarcinoma of the large intestine ALI, Lewis lung cancer, melanoma B-16, and sarcoma 37). Simultaneous administration of MTX and methylcobalamine enhanced the inhibition of Ca 755 growth and increased the duration of survival of tumor-bearing C57Bl mice. MTX in combination with MCA antagonist methylcobalamine chloropalladate produced more marked inhibition of the growth of Ca 755 and CC 5 than MTX alone. Enhanced inhibition of the growth of AC 755, CC 5, and ALI was also recorded after combined administration of MTX and inhibitor of methionine synthetase. (34 Refs) (In RUS)

24. EFFECT OF MITOMYCIN-C AND ADRIAMYCIN ON CULTURED HUMAN HEPATOMA CELL CYCLE PROGRESSION.

Sano H, Sasaki F, Une Y, Hata Y, Nakanishi Y, Uchino J, Kasai Y
First Dept. Surgery, Hokkaido Univ. Sch. Medicine, Sapporo, Japan
Gan No Rinsho; 27(10):1200-1204,A-57 1981

Eighth generation C-HC-20 cultured human hepatoma cells with a population doubling time of 30.4 hr were separated into individual culture bottles containing 2 x 10(4) cells/2 cc and were treated with mitomycin C (MMC) and/or adriamycin (ADR). Histograms of the cultured cells were made hr 48 and 72 after treatment. On the basis of a standard human dosage of the MMC (4 mg) or the ADR (10 mg), the cells were treated with MMC (20, 2, 0.2, or 0.02 ug/ml) and/or ADR (50, 5, 0.5, or 0.05 ug/ml). Hr 48 after a 1-hr exposure to the MMC, a marked increase in G2-M phase cells were observed with low concentrations of the MMC. Continuous or 1-hr exposure of the cells to the ADR resulted in an increase in G2-M phase cells for up to hr 72 after treatment. On the basis of the results, it was hypothesized that administration of ADR during the 48 hr period after 1-hr administration of low-dose MMC would result in enhanced effects. (17 Refs) (In JPN)

25. RESPONSE OF L1210 LEUKEMIA TO TREATMENT WITH 1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA PLUS 4'-DEMETHYLEPIPODOPHYLLOTOXIN-9-(4,6-O-2-THENYLIDENE BETA-D-GLUCOPYRANOSIDE).

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Cancer Res; 41(10):3891-3895 1981

Mice, inoculated ip with 1 million L1210 ascites cells, were treated subsequently with 1,3-bis(2-chloroethyl)-1-nitrosourea plus 4'-demethylepipodophyllotoxin-9-(4,6-O-2-thenylidene beta-D-glucopyranoside) in various combinations of dosages. The drugs were administered ip in rapid succession on one of four schedules. When treatment was administered on day 1, 24 hr after inoculation, all mice treated with 1 of 5 combinations of dosages survived for 60 days, apparently free of leukemia, and another 16 combinations of the drugs cured 50%, or more, of the animals. Treatment with combinations of lower dosages of the drugs on days 1, 4, and 7 was as effective as treatment with larger dosages on day 1; all mice treated with 5 combinations of the drugs survived, and 17 other combinations cured 50%, or more, of the mice. When mice were treated on similar schedules but the initiation of treatment was delayed until day 4, the therapeutic efficacy of the individual drugs and of the combinations decreased. Some of the mice survived for 60 days after treatment with both drugs on day 4, but the incidence was not greater than that achieved by treatment with the optimal dosage of 1,3-bis(2-chloroethyl)-1-nitrosourea on day 4. The schedule of treatment on days 4, 7, and 10 was the least effective, therapeutically, of the four schedules tested; only 12 of 235 mice survived for 60 days after treatment with the individual drugs or the drug combination. Because of a termination of the studies after 60 days, the data for all four studies were analyzed by the Cox multiple-regression technique. By this criterion, the incidence of mortality after treatment with the drugs on either day 1 or days 1, 4, and 7 was attributable in part to a therapeutic interaction between the drugs. This therapeutic interaction was not observed when mice were treated once on day 4. Analysis of the incidence of mortality after three courses of treatment, ie, treatment on days 4, 7, and 10, indicated that, although each drug was oncolytic, an interaction between the drugs reduced the effectiveness of the combination. 4'-demethylepipodophyllotoxin-9-(4,6-O-2-thenylidene beta-D-glucopyranoside) plus 1,3-bis(2-chloroethyl)-1-nitrosourea was remarkably effective for the treatment of L1210 leukemia, and on certain schedules the effectiveness resulted from a therapeutic interaction between the drugs. (Author abstract) (36 Refs)

26. SCHEDULE-DEPENDENT SYNERGISM OF COMBINATIONS OF HYDROXYUREA WITH ADRIAMYCIN AND 1-BETA-D-ARABINOFURANOSYLCYTOSINE WITH ADRIAMYCIN.

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Cancer Res; 41(10):3881-3884 1981

The lethal effects of combinations of adriamycin (ADR) and either hydroxyurea (HU) or 1-beta-D-arabinofuranosylcytosine (ara-C) were studied in relation to a drug-scheduling interval in Sarcoma 180 cells grown in vitro. Drug lethality was determined by cell cloning in soft agar. Serial kinetic changes induced by a priming dose of HU or ara-C were monitored by flow cytometry and related to schedule-dependent cell killing by ADR. All drug exposures were for 1 hr. When ADR was given together with either HU or ara-C, cell log kill was additive. However, when ADR was given after exposure to either HU or ara-C, cell killing was increased up to 200-to 500-fold, respectively. Max schedule-dependent synergism was observed at a drug-scheduling interval of 2 hr; schedule-dependent synergism decreased as the interval between drugs was increased beyond 2 hr. Schedule-dependent synergism was not observed when the same drug combinations were given in reversed order. Drug-induced changes in the DNA histogram were not seen until 5 hr after HU exposure and 8 hr after ara-C exposure. Thus, the schedule-dependent synergism between ADR and either HU or ara-C cannot be explained by cell cycle blockade with synchronization of cells in S phase. (Author abstract) (24 Refs)

27. REVERSAL OF RESISTANCE TO METHOTREXATE BY HYPERTHERMIA IN CHINESE HAMSTER OVARY CELLS.

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Cancer Res; 41(10):3840-3843 1981

Our Chinese hamster ovary cells are extremely resistant to methotrexate (MTX) (100% survival after 500 ug/ml for 13 hr). However, exposure to 43 C (but not 41 C or 42 C) for 1 hr sensitizes the cells to MTX so that a 50% cell kill in excess of that due to hyperthermia occurs. Treatment of cells at 43 C increases net MTX uptake by about 30% at 30 min but causes a substantial reduction after 1 hr. This negative effect is greater in cells continually heated at 43 C than in those exposed for only 1 hr. Treatment at 43 C for 1 hr also markedly increases efflux of MTX out of cells over the first 2 hr. Dihydrofolate reductase activity was found to decrease to about 50% of control values by 4-5 hr after exposure to 43 C. The biological half-life of dihydrofolate reductase in Chinese hamster ovary cells was determined to be about 4.5 hr, indicating that hyperthermia-induced cessation of protein synthesis may explain both the decrease in dihydrofolate reductase activity and the sensitization to MTX observed with heat exposure. In scheduling experiments, lethality due to exposure to 43 C for 1 hr in conjunction with MTX was max when 1-hr drug exposure began just at the end of heat treatment. (Author abstract) (23 Refs)

28. CYTOKINETIC AND CYTOTOXIC EFFECTS OF ANTIMETABOLITES ON 9L RAT BRAIN TUMOR CELLS IN VITRO.

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Cancer Res; 41(10):3835-3839 1981

Treatment of exponentially growing 9L monolayer cells with graded concentrations of methotrexate or 5-fluorouracil (5-FU) resulted in approx 95% cell kill, corresponding to the percentage of cells in this system labeled by autoradiography (98%). Additional cell kill could be obtained if 5-FU was administered at a high concentration (7.7 x 10(-4) M) and could be partly reversed in the presence of (8.2 x 10(-5) M) uridine. When cell kill was measured as a function of time of exposure (a 3-hr exposure to 2.2 x 10(-4) M), methotrexate or 7.7 x 10(-6) or 7.7 x 10(-4) M 5-FU killed 30 to 50% of the cell population, which is equivalent to the percentage of the S-phase cells of the system. With both agents, additional cell kill was offset by division of unaffected G2 cells and a drug-induced block of G1 cells at the G1-S border, and it depended on long drug exposure. Nontoxic concentrations of 5-FU could synchronize and increase the fraction of cells in the drug-sensitive S phase. (Author abstract) (19 Refs)

29. ENHANCED CYTOTOXICITY OF ANTINEOPLASTIC AGENTS FOLLOWING PROLONGED EXPOSURE TO MISONIDAZOLE.

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Br J Cancer; 44(2):201-207 1981

Chinese hamster V79 cells cultured in vitro were used to investigate the cytotoxicity of various anti-cancer drugs subsequent to a prolonged treatment of the cells with misonidazole (MISO). The sensitivity of the cells to Bleomycin, Melphalan or Cisplatin was significantly increased by prior incubation with MISO under hypoxic conditions. When cysteamine, a radical scavenger, was present during the pretreatment with MISO, this enhancement of cytotoxicity was greatly reduced. These experiments, suggest that MISO by virtue of its selective toxicity towards hypoxic cells and its enhancement of cell killing by anti-neoplastic drugs, can play an important role in cancer chemotherapy. (Author abstract) (26 Refs)

30. COMBINATION THERAPY OF A MOUSE SARCOMA USING RAZOXANE AND ELECTRON IRRADIATION.

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Br J Cancer; 44(1):117-123 1981

The combination of a single dose of razoxane (ICRF 159) with a single dose of electron radiation has been studied with the murine sarcoma S180. A drug dose of 30 mg/kg combined with radiation produced a greater tumor response than either agent alone, but it was not possible to establish whether the effect was more than additive. Direct measurements of tumor and sc oxygen concentrations and studies of tumor-cell respiration were carried out after various razoxane treatments in an attempt to elucidate mechanisms of action. There were no indications at the drug dose levels used in the radiation studies of any significant changes in tissue oxygenation or cellular respiration. (Author abstract) (21 Refs)

31. EXPERIMENTAL STUDIES ON THE RADIATION-MODIFYING EFFECT OF BLEOMYCIN IN MALIGNANT AND NORMAL MOUSE TISSUE IN VIVO.

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Cancer Treat Rep; 65(7/8):583-589 1981

The interaction between bleomycin (BLM) and radiation was studied in a C3H mammary carcinoma and its surrounding normal skin. In the skin, single and fractionated doses of sequential treatment with BLM (25 mg/kg) 24 hr prior to radiation therapy did not influence the response to irradiation, whereas simultaneous treatment with BLM given 15 min before radiation therapy enhanced the reaction to irradiation by a factor of 1.2 or 1.4 following treatment with one fraction or five fractions, respectively. The tumor response to irradiation was not influenced by a single sequential treatment, but five daily fractions of irradiation therapy following five daily dose fractions of BLM increased the radiation dose needed to control 50% of the tumors, probably because the tumors continued to grow during the BLM treatment. Simultaneous treatment enhanced the response to irradiation by a factor of 1.2 after both single-dose and fractionated therapy. Based on these data it was concluded that none of the combined treatment schedules were able to produce a better therapeutic effect than radiation therapy alone. Furthermore, mortality due to lung fibrosis in mice treated with BLM indicated the marked toxicity of the drug. This toxicity was most pronounced after fractionated treatment and when radiation therapy and BLM were given simultaneously. (Author abstract) (27 Refs)

32. COMPARISON OF HYPERBARIC OXYGEN AND MISONIDAZOLE IN FRACTIONATED IRRADIATION OF MURINE TUMORS.

Suit HD, Maimonis P, Michaels HB, Sedlacek R
Edwin L. Steele Lab. Radiation Biology, Dept. Radiation Medicine, Massachusetts General Hosp., Harvard Medical Sch., Boston, MA, 02114
Radiat Res; 87(2):360-367 1981

The enhancement ratios for hyperbaric oxygen and for misonidazole were determined using two transplanted syngeneic tumors (spontaneous mammary carcinoma and squamous cell carcinoma) in C3Hf/Sed mice, and the acute response of C3H mouse skin as the endpoints. Animals were irradiated when tumors reached 6-8 mm in size or 18 days after plucking hair of the right-leg thigh of tumor-free mice. Calculation of the radiation dose (which produced a local control of 50% of tumors) showed essentially the same enhancement ratios (1.45-1.55) for hyperbaric oxygen and misonidazole (0.3 mg/kg, ip). The response of normal mouse skin to radiation given in five equal doses indicated slightly greater enhancement ratio for hyperbaric oxy gen (1.94) than for misonidazole (1.54). (26 Refs)

33. SYNERGISTIC ANTILEUKEMIC ACTIVITY OF COMBINATIONS OF TWO NITROSOUREAS.

Wheeler GP, Schabel FM, Trader MW
Biochemistry Dept., Southern Res. Inst., 2000 9th Ave., Birmingham, AL, 35255
Cancer Treat Rep; 65(7/8):591-599 1981

A rationale based on known chemical, biochemical, and biologic properties of nitrosoureas led to the testing of combinations of lomustine (CCNU) with chlorozotocin for in vivo activity against L1210 leukemia. Several combinations yielded synergistic antileukemic activity. (Author abstract) (12 Refs)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

34. ULTRASTRUCTURAL LOCALIZATION OF CA++ AND ITS POSSIBLE ROLE IN THE AMELIORATION OF KIDNEY TOXICITY DUE TO CISPLATIN.

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Dept. Zoology, Michigan State Univ., East Lansing, MI, 48824
J Clin Hematol Oncol; 11(3):73-84 1981

Hydrolysis products of cisplatin under low chloride ion concentrations induce an efflux of accumulated Ca++ from within the mitochondria of the renal proximal tubule cells as demonstrated by electron histochemical methods. Ca++ when bound to the plasma membrane changes its permeability to Na+ and Cl- ions. The resultant increase in Cl-ions reverts the hydrolysis products back to inactive cisplatin which is excreted through the urine, which explains the amelioration of kidney toxicity through hydration using normal physiological saline soln. (Author abstract) (36 Refs)

35. DETERMINANTS OF THE TOXICITY OF L-ALANOSINE TO VARIOUS ORGANS OF THE MOUSE.

Tyagi AK, Thake DC, McGee E, Cooney DA
Lab. Biochemical Pharmacology, Natl. Inst. Arthritis, Metabolism, and, Digestive Diseases NIH, Bethesda, MD, 20205
Toxicology; 21(1):59-69 1981

Male and female BDF1 mice were given 2 ip injections, 1 hr apart,of the antitumor antibiotic L-alanosine (L-2-amino-3-[N-hydroxy,N-nitrosamino]propionic acid). Tissues were assayed for 5-amino-4-imidazole-N-succinocarboxamide ribonucleotide synthetase (SAICAR synthetase), adenylosuccinate synthetase, adenylosuccinate lyase, and L-alanosine and its metabolites. The LD50 of L-alanosine was about 2 g/kg. In general the greatest toxicity occurred in L-5178Y/AR tumor tissue, followed by small intestine, lung, liver, and spleen. The concentration of a antimetabolite of L-alanosine, L-alanosyl-5-amino-4-imidazole carboxylic acid ribonucleotide (L-alanosyl AICOR) correlated with toxicity, supporting the belief that this molecule is responsible for the toxic and therapeutic effects of L-alanosine. The correlation is less perfect for SAICAR synthetase, the enzyme which produces L-alanosyl AICOR, because of the effects of adenylosuccinate lyase, which decomposes L-alanosyl-AICOR. Apparently the interaction of the synthesizing enzyme, catabolizing enzyme, and target enzyme determine whether L-alanosyl AICOR occurs in sufficient concentration to cause cellular damage. (13 Refs)

36. CYST FORMATION IN RAT KIDNEY INDUCED BY CIS-PLATINUM ADMINISTRATION.

Dobyan DC, Hill D, Lewis T, Bulger RE
Dept. Pathology and Lab. Medicine, Univ. Texas Health Science Center, Post Office Box 20708, Houston, TX, 77025
Lab Invest; 45(3):260-267 1981

The long-term pathologic effects of the antitumor drug cis-diamminedichloroplatinum II (CP) on the structure of the rat kidney were investigated. Light microscopy and transmission and scanning electron microscopy were used to characterize the morphologic changes 2 wk, 4 wk, and 6 mo after ip injection of CP to rats. At all time intervals examined, the S3 segment of the proximal tubule located in the outer stripe of the medulla showed the most consistent pattern of injury. Two wk after CP, the proximal tubules located in the outer stripe region as well as the medullary rays were widely dilated and lined by low-lying epithelial cells, many of which contained large atypical nuclei. Many tubules still showed evidence of necrosis, whereas other tubules appeared to be undergoing atrophic changes. After 4 wk, proximal tubular dilation continued resulting in the formation of numerous microcysts in the region of the outer stripe. These changes appeared to progress, and after 6 mo large cysts (mean diameter 2,152 +-1,241 um) were identified which involved the entire outer stripe, with many of these cysts extending to the subcapsular cortex. The kidneys at this time period showed a pattern of chronic renal injury in the outer stripe, and this damage was now also observed in the cortex. In several animals, small foci of abnormal foam cells surrounded by a basal lamina could be identified. We conclude that CP has a pronounced long-term effect and causes cyst formation in the rat kidney. (Author abstract) (22 Refs)

37. CYTOTOXICITY OF CISPLATIN IN RAT INTESTINE.

Choie DD, Longnecker DS, Copley MP
Lab. Chemical Pharmacology, NCI, NIH, Building 37, Room 5A13, Bethesda, MD, 20205
Toxicol Appl Pharmacol; 60(2):354-359 1981

The cytotoxicity of cisplatin (cis-dichlorodiammineplatimun II; single doses of 5 mg/kg) was studied in the gastrointestinal mucosa of 344 male Fischer rats. Animals had diarrhea on days 1-3 after treatment. In the duodenum less than 10% of the crypts showed necrosis 1 day after treatment. Mitosis was reduced to 50% of control levels on days 1 and 2, but rose to normal on day 3 and above normal on day 4. The jejunum showed necrosis in approx 30% of the crypts on day 1. Mitosis was reduced by 67%. Remaining cells were flattened, and many crypts were atrophied. Mitosis increased on day 3. The lining of the jejunum was nearly normal by day 5. The ileum showed the most extensive damage. On day 1 about 50% of the crypts had necrotic cells. Mitosis was severely restricted. On days 2 and 3 most crypts were atrophic, and villi were shortened. On days 3-5 the lining of the ileum was regenerated, with many villi showing irregular forms. Platinum assays showed no preferential accumulation in any areas of the small intestine. The stomach and large intestine were largely unaffected by cisplatin. Evidently cisplatin preferentially acts on proliferating cells in the crypts of the small intestine. (21 Refs)

38. ETHANOL-INDUCED CELL SENSITIZATION TO BLEOMYCIN CYTOTOXICITY AND THE INHIBITION OF RECOVERY FROM POTENTIALLY LETHAL DAMAGE.

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Dept. Antibiotics, Natl. Inst. Health, Shinagawa-ku, Tokyo 141, Japan
Cancer Res; 41(10):4111-4114 1981

The cytotoxic effect of bleomycin toward mouse mammary carcinoma FM3A cells in culture was markedly potentiated by exposure of the cells to ethanol either before or after treatment with bleomycin. Ethanol-induced cell sensitization to bleomycin cytotoxicity produced a decrease in cell survival which became dependent on dose and time of drug treatment. The sensitizing effect of ethanol after drug treatment was max when ethanol exposure immediately followed drug treatment, and it rapidly decreased as the time interval between the two treatments was increased. Ethanol did not sensitize cells to the cytotoxic effects of cis-diamminedichloroplatinum(II) and macromomycin. These results are discussed in terms of the ability of ethanol to inhibit cell recovery from potentially lethal damage after bleomycin treatment. (Author abstract) (29 Refs)

39. APPLICATION OF SMALL DOSES IN ANTITUMOR CHEMOTHERAPEUTIC DRUGS IN EXPERIMENT.

Garkavi LKh, Kvakina EB, Mulatova AK, Tarasjants FM
Res. Inst. Oncology, RSFSR Ministry Public Health, Rostov-on-the Don, USSR
Vopr Onkol; 27(7):61-66 1981

The susceptibility of tumor tissue to therapeutic and smaller doses of chemotherapeutic drugs was assessed on the basis of SH-group inhibition in vitro. As therapeutic dose was decreased, rhythmic changes of tumor susceptibility were observed. In the experiments on tumor-bearing rats, the small dose of chemotherapeutic agent, which in preliminary in vitro experiments proved to be as effective as the therapeutic one (1/5 therapeutic dose), was found to cause the same suppression of tumor growth. However, it did not induce leukopenia, lymphopenia, thymus involution or any other manifestations of stress which followed multiple injections of therapeutic doses. The WBC and thymus indices in rats, which received the small dose, suggest the development of reactions of training and activation which increase the nonspecific resistance of the organism. (Author abstract) (15 Refs) (In RUS)

40. ON HOMOPOIETIC RESISTANCE TO THE DAMAGING EFFECT OF CYTOSTATIC SUBSTANCES IN CASES OF DRUG-RESISTANT TUMORS.

Rakhimov KD, VermenichevSM, Kabiev OK
Kazakh Res. Inst. Oncology and Radiology, Alma-Ata, USSR
Vopr Onkol; 27(7):57-61 1981

The effect of chemotherapy on peripheral blood indices in rats with drug-resistant tumors was studied. It was found that treatment of polyphenolic preparation of Leukoephdin or a combination of antitumor drugs aimed at suppressing the resistance of Pliss' lymphosarcoma to rubomycine did not cause any disturbances in blood morphology which occur in rats with basic tumor strains. (Author abstract) (11 Refs) (In RUS)

PHARMACOKINETICS OF ANTITUMOR AGENTS

41. ASSAY FOR METHOTREXATE IN NANOMOLAR CONCENTRATIONS WITH SIMULTANEOUS DETECTION OF CITROVORUM FACTOR AND VINCRISTINE.

Deen WM, Levy PF, Wei J, Partridge RD
Dept. Chemical Engineering, Massachusetts Inst. Technology, Cambridge, MA, 02139
Anal Biochem; 114(2):355-361 1981

A new assay procedure has been developed for methotrexate in plasma samples, using high-pressure liquid chromatography with fluorescence detection. A novel feature of this procedure is the reduction of methotrexate with dithionite to yield a highly fluorescent product, tentatively identified as 2,4-diamino-6-methylpteridine. Simultaneous detection of citrovorum factor (folinic acid) by fluorescence has also been demonstrated, and detection of vincristine by UV absorption. The procedure is suitable for simultaneous measurement of methotrexate, citrovorum factor, and vincristine in plasma samples at concentrations as low as 5 X 10(-9), 10(-6), and 10(-7) M, respectively. Sample preparation time is approx 45 min, and elution time about 30 min. (Author abstract) (26 Refs)

42. STRUCTURE-PHARMACOKINETIC RELATIONSHIPS FOR MISONIDAZOLE ANALOGUES IN MICE.

Workman P, Brown JM
MRC Clinical Oncology and Radiotherapeutics Unit, Medical Res. Council Centre, Medical Sch., Hills Road, Cambridge, CB2 2QH, England
Cancer Chemother Pharmacol; 6(1):39-49 1981

The influence of lipophilicity on renal and metabolic clearance, pharmacokinetic dose-dependence, and the effects of hepatic microsomal enzyme induction with phenobarbitone were examined for six farily closely related analogs of misonidazole (MISO) in adult male BALB/c mice. The analogs were all uncharged at physiological pH and had very similar electron affinities. Peak blood concentrations of all the analogs studied, with the exception of SR-2508 and SR-2555, were generally similar for equimolar doses injected ip. Analogs as lipophilic and more lipophilic than MISO (partition coefficient = 0.43) exhibited dose-dependent elimination kinetics: clearance was slower and apparent elimination half-life longer at high doses. This behavior was most marked with the lipophilic analog Ro 07-0913, which was cleared 13 x faster at the low dose than at the high dose. With analogs more hydrophilic than MISO the elimination half-life was not dose-dependent. A good correlation was observed between the partition coefficient and urinary excretion, the amount of unchanged drug excreted in the urine decreasing with increasing lipophilicity. The results appeared to be consistent with model previously proposed which suggested that lipophilic analogs are cleared mainly by inducible hepatic microsomal metabolism and exhibit dose-dependent elimination kinetics as a result of saturation of metabolizing enzymes by the high drug concentration achieved with large doses. (35 Refs)

43. PHARMACOKINETICS OF HEXAMETHYLMELAMINE AND PENTAMETHYLMELAMINE IN MICE.

Broggini M, Colombo T, D'Incalci M, Donelli MG, Gescher A, Garattini S
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Cancer Treat Rep; 65(7/8):669-672 1981

Plasma pharmacokinetics of hexamethylmelamine (HMM) and pentamethylmelamine (PMM) were investigated after ip administration of doses of 50 or 100 mg/kg to M5076/73A ovarian tumor-bearing C57BL/6J female mice. The half-life of HMM was 44.5-49 min; the half-life of PMM was 7.6-8.7 min. The area under the concentration-vs-time curve (AUC) was also much higher for HMM than for PMM. The AUC for the metabolite N2,N2,N4,N6-tetramethylmelamine (TMM) was 7 to 10x higher than that of the parent compounds. After incubation with mouse liver microsomes and cofactors, the rates of metabolism of HMM and PMM were essentially the same. Plasma protein binding was 94%, 71%, and 50% for HMM, PMM, and TMM, respectively. (Author abstract) (10 Refs)

44. DISTRIBUTION OF RADIOACTIVITY AND ANTHRACYCLINE-FLUORESCENCE IN TISSUES OF MICE ONE HOUR AFTER (14C)-LABELED AD32 ADMINISTRATION: EVIDENCE FOR TISSUE AGLYCONE FORMATION.

Israel M, Karkowsky AM, Khetarpal VK
Div. Pharmacology, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Cancer Chemother Pharmacol; 6(1):25-30 1981

The radioactivity and anthracycline fluorescence in tissues of male A/JAX mice 1 hr after administration of a dose of AD 32, a disubstituted analog of adriamycin, was examined. In general, the levels of materials as determined by either method were approx the same. Levels of radioactivity appeared to be slightly higher than fluorescence in pancreas, spleen, heart, and skeletal muscle. Levels of fluorescence were higher than the levels of radioactivity in the small intestine. Of the tissues studied, the highest levels of both fluorescence and radioactivity were found in the small intestine. High pressure liquid chromatography analysis of extracts of liver and small intestine, prepared from tissues of mice sacrificed 1 hr after treatment with AD 32, revealed N-trifluoroacetyladriamycin (AD 41, the predominant fluorescent species), N-trifluoroacetyladriamycinol (AD 92), trace amounts of AD 32, and two new metabolites, designated unknowns 1 and 2. Further analysis of these unknowns, which appear to be aglycones, is described. (13 Refs)

45. PHARMACOKINETICS AND ORGAN DISTRIBUTION OF METHOTREXATE IN THE RAT.

Scheufler E, Zetler G, Iven H

Institut fur Pharmakologie, Medizinische Hochschule, Ratzeburger Allee 160, D-2400 Lubeck, W. Germany

Pharmacology; 23(2):75-81 1981

After iv injection of 31 mg/kg methotrexate (MTX), its concentrations were determined in plasma, liver, kidney, bone marrow, stomach, duodenum, jejunum, colon and muscle up to 23 days, using an enzymatic assay. Plasma pharmacokinetics were described by a triexponential function, with a terminal half-life of 4.2 hr. Up to 1.5 hr after injection, the initial rapid decline of MTX concentrations in bone marrow, kidney, and liver roughly paralleled that in plasma. The terminal half-life of MTX in bone marrow was greatly prolonged (37 hr), while MTX remained nearly constant in liver (0.57 ug/ml) and kidney (0.53 ug/ml) from 6 hr to 23 days. In the intestines, luminal as well as tissue MTX concentrations were determined. The stomach showed a triexponential decay of tissue MTX and low luminal concentrations throughout. In the duodenum, the middle of jejunum, and the colon tissue MTX seemed to follow a bi- or triexponential function. However, high luminal concentrations due to MTX biliary excretion, when reaching a given intestinal portion, increased the MTX tissue concentration in this segment. (Author abstract) (18 Refs)

46. THE PHARMACOKINETICS OF PREDNIMUSTINE AND CHLORAMBUCIL IN THE RAT.

Newell DR, Shephard CR, Harrap KR

Dept. Biochemical Pharmacology, Inst. Cancer Res., Belmont, Sutton, Surrey, England

Cancer Chemother Pharmacol; 6(1):85-91 1981

The comparative pharmacokinetics and tissue distributions of chlorambucil (CB) and prednimustine (PNM) were examined. Metabolic studies were performed in Walker 256 carcinosarcoma-bearing female Wistar rats while toxicity studies were performed in non-tumor bearing rats. Following CB (10 mg/kg) or PNM (20 mg/kg) administration, the total of drug-derived materials were higher in the plasma than in any of the tissues examined at all time points, with the exception of the intestine. The plasma levels of CB and phenyl acetic mustard detected following sc injection of CB or PNM were determined. The methyl ester of CB was much less toxic than CB and was also less toxic than an equimolar dose of PNM. Multiple low doses of CB were much less toxic than the single high dose. Multiple low doses of CB did not kill CB-resistant tumor cells. Neither did the methyl ester of CB. However, multiple doses of CB plus prednisolone were as effective as PNM, killing 43% of the resistant tumor cells. (20 Refs)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

47. ANTI-TUMOUR ACTIVITY OF NOVEL ADDUCTS OF ASCORBIC ACID WITH ALDEHYDES.

Elvin P, Slater TF

Dept. Anatomy and Experimental Pathology, Univ. St. Andrews, Bute Medical Buildings, St. Salvatore's Coll., St. Andrews, KY169TS Fife, Scotland

Eur J Cancer Clin Oncol; 17(7):759-765 1981

A novel adduct of ascorbic acid and methylglyoxal (MGA) inhibited the growth of the Ehrlich ascites carcinoma (EAC) in male CBA/Ca mice, following the ip injection of 5 x 10(6) tumor cells on day 0. MGA, 62.5 and 125 mg/kg-1 twice daily ip, inhibited tumor growth by 93% and 96%, respectively, when given on days 1-5 following transplantation. Treatment with MGA over days 5-9 after tumor cell injection was ineffective. A modified dose schedule, MGA 250 mg kg-1 ip, given as a single ip dose on days 1, 3 and 5 following transplantation, significantly increased the survival time of EAC-bearing mice. A number of related ascorbate (AsA) acetals were tested for antitumor activity using an identical experimental protocol. AsA-acetylacrolein was as active a growth inhibitor as MGA, inhibiting the growth of EAC by 97 and 98% (100 and 200 mg kg-1 twice daily, respectively). AsA-acrolein and AsA-glyoxal also inhibited the growth of EAC. Under identical conditions ascorbic acid, 200 mg kg-1 ip, twice daily, did not inhibit the growth of EAC, while the aldehydes methylglyoxal, 50 mg kg-1, and acetylacrolein, 12.5 mg kg-1, inhibited tumor growth by 98 and 99%, respectively. Combination of the aldehydes with ascorbic acid resulted in a considerable reduction in host toxicity; the LD50 for MG being 332 mg kg-1 and that for MGA 959-1,462 mg kg-1, for a single ip dose in mice. (Author abstract) (37 Refs)

48. 1-DEAZA-7,8-DIHYDROPTERIDINES, A NEW CLASS OF MITOTIC INHIBITORS WITH ANTICANCER ACTIVITY.

Wheeler GP, Bowdon BJ, Werline JA, Temple C

Kettering-Meyer Lab., Southwestern Res. Inst., Birmingham, AL, 35255

Biochem Pharmacol; 30(16):2381-2384 1981

Ethyl 5-amino-1,2-dihydro-3-[(N-methylanilino)methyl] pyrido[3,4-b]pyrazin-7-ylcarbamate (NSC-181928), a 1-deaza-7,8-dihydropteridine, was tested for its ability to cause the arrest of cultured tumor cells in mitosis. The drug was added to 24-hr-old cultures of leukemia 1210 cells, leukemia P388/0, cells and vincristine-resistant P388/VCR cells and to 48-or 72-hr-old cultures of other cell lines including plastic-attached cultures of murine colon tumors number 26 (ip implanted) and number 38 (sc implanted). The cells were harvested at selected times, washed, and used for the preparation of microscopic slides. After the slides were stained with toluidine blue, 1,000 cells/slide were counted and classified as interphase or mitotic. NSC-181928 was active against all cell lines tested. Its effect was quantitatively similar to that of VCR and vinblastine (VB) for P388/0, colon tumor number 26 cells, and colon tumor number 38 cells. Its activity against P388/VCR was similar to that of VB and similar to its activity against P388/0. These results demonstrated that NSC-181926 can prevent the progression of cells through mitosis. (16 Refs)

49. SOME TOXICITIES OF TRIPTOLIDE IN MICE AND DOGS.

Cheng YL, Ye J, Lin D, Lin L, Zhu J

Inst. of Medical and Pharmaceutical Sci. of Fujian, Fuzlore, People's Republic of China

Zhongguo Yaoli Xuebao; 2(1):70-72 1981

Triptolide, isolated from Tripterygium wilfordii, has been demonstrated to have marked inhibitory effects on murine leukemia (L1210, P388, and L615) and human nasopharyngeal carcinoma (KB) cells. Its toxicities are described in mice and dogs. The LD50 in mice were determined to be 0.8 mg/kg (iv) and 0.8 mg/kg (ip). In dogs, the lethal dose was 160 ug/kg which also suppressed the bone marrow; at 40 and 80 ug/kg, triptolide exhibited reversible toxic effects on the heart, hematopoiesis and the gastrointestinal tract, while a dose of 20 ug/kg showed no toxicity. The cause of death in dogs was mainly due to liver and heart damage. No delayed toxicity was observed in dogs 6 wk after triptolide withdrawal. (7 Refs) (In CHI)

50. ALKYLATING NUCLEOSIDES. 7. N-GALACTO AND N-MANNOPYRANOSYL-(HALOMETHYL)-1, 2,3-TRIAZOLES.

de las Heras FG, Sanchez-Perez RM, Aguado ML

Instituto de Quimica Medica, Juan de la Cierva 3, Madrid-6, Spain

Eur J Med Chem Chim Ther; 16(4):339-344 1981

Galactopyranosyl and mannopyranosyl derivatives of 1,2,3-triazole alkylating nucleosides were prepared in order to study whether these hexopyranosyl moieties, such as the glucopyranosyl, also give alkylating compounds with high cytostatic activities. 4-Bromomethyl-1,2,3-triazole glycoside and 4-iodomethyl-1,2,3-triazole glycoside inhibited the in vitro growth of HeLa cells and increased the life span of mice bearing Ehrlich carcinoma ascites tumors but not of mice bearing L-1210 lymphoid leukemia. (22 Refs)

51. NEW ANTITUMOR ANTIBIOTICS 5590 AND 2928.

Gauze GF, Maksimova TS, Ol'khovatova OL, Laiko AV, Selezneva TI, Brazhnikova MG, Konstantinova NV, Tolstykh IV, Fedorova GB, Borisova VN, Rubasheva LM, Katrukha GS, Bazhanov VS

All-Union Res. Inst. Screening for New Antibiotics, Moscow, USSR

Antibiotiki; 26(7):483-488 1981

Biosynthesis, isolation, and activity of new actinomyces antibiotics 5590 and 2928 are described. Analysis of UV and infrared spectra of hydrolysates indicated that 5590 and 2928 belonged to a class of chromophore-containing peptides. Antitumor activity of antibiotics was tested in random-bred albino mice with transplanted solid lymphosarcoma (LIO-1), solid sarcoma 180, and ascites lymphadenosis NK/Ly. The sc administration of 5590 at 50 and 62.5 ug/kg provided a 56% and 76%, respectively, inhibition of sarcoma 180. The iv administration of 5590 provided a 50% inhibition of LIO-1 and NK/Ly growth at 18.5 and 15.1 ug/kg, respectively (max permissible doses), while 90% inhibition of tumor growth requi red administration of 5590 at LD50. The sc administration of 2928 at 50-200 ug/kg (max permissible doses) provided a 50% inhibition of LIO-1 and sarcoma 180 growth, and 80% inhibition of NK/Ly growth; the iv and ip administration of 2928 was ineffective and was associated with significant toxicity. (2 Refs) (In RUS)

52. RUBEOMYCIN, A NEW ANTRACYCLINE ANTIBIOTIC COMPLEX. I. TAXONOMY OF PRODUCING ORGANISM, ISOLATION, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF RUBEOMYCIN A, A1, B AND B1.

Ogawa Y, Sugi H, Fujikawa N, Mori H

Central Res. Lab., Ishihara Sangyo Kaisha, Ltd., 3-1, 2-chome, Nishi-Shibukawa, Kusatsu-city, Shiga-ken, Japan

J Antibiot (Tokyo); 34(8):938-950 1981

A new antibiotic complex has been obtained from the cultures of an actinomycete, strain FA-1180, isolated from a soil sample collected at lake side of Biwa in Japan. On the basis of taxonomic studies the producing microorganism is designated as Actinomadura roseoviolacea var biwakoensis nov var The antibiotic complex belongs to the class of anthracycline glycoside antibiotics. All components form deep red fine needles on crystallization; components are named rubeomycin A, rubeomycin A1, rubeomycin B and rubeomycin B1. These components exhibit activity against Gram-positive bacteria as well as Yoshida sarcoma cell in vitro. These components are also effective on P388 leukemia. (Author abstract) (8 Refs)

53. FOLATE ANALOGUES ALTERED IN THE C(9)-N10 BRIDGE REGION. 18. SYNTHESIS AND ANTITUMOR EVALUATION OF 11-OXAHOMOAMINOPTERIN AND RELATED COMPOUNDS.

Nair MG, Bridges TW, Henkel TJ, Kisliuk RL, Gaumont Y, Sirotnak FM

Dept. Biochemistry, Coll. Medicine, Univ. South Alabama, Mobile, AL, 36688

J Med Chem; 24(9):1068-1073 1981

The chemical synthesis of 11-oxahomoaminopterin(1) has been carried out using procedures which were also found to be applicable to the synthesis of 11-oxahomofolic acid(2). Reaction of 1-bromo-4-[p-(carbomethoxy)phenyoxy]-2-butanone(10) with sodium azide gave 1-azido-4-[p-(carbomethoxy)phenoxy]-2-butanone(11). Protection of the carbonyl group of 11 as the ethylene ketal and subsequent base hydrolysis of the product gave 1-azido-4-(p-carboxyphenoxy)-2-butanone ketal(13). The glutamate conjugate 14 was prepared from 13 by the isobutyl chloroformate method and was hydrogenated to diethyl N-[(alpha-amino-2-oxo-4-butanoyl)-p-anisoyl]-L glutamate ketal(15). Reaction of 15 with 6-chloro-2,4-diamino-5-nitropyrimidine(16) and 2-amino-6-chloro-4-hydroxy-5-nitropyrimidine(17) and deprotection of the corresponding products gave the intermediates 18 and 19, which were elaborated to 1 and 2 using a series of steps involving deprotection, dithionite reduction, cyclization, oxidation, and hydrolysis. Although 11-oxahomoaminopterin showed antifolate activity against two folate-requiring microorganisms and inhibited Lactobacillus casei DHFR, it was inactive against L-1210 leukemia in mice at a max dose of 48 mg/kg. Compound 1 was also tested for its ability to be transported via the methotrexate transport system using the L-1210 and Ehrlich tumor cell lines, and these results are compared with those of related analogues. The growth inhibitory activity of 1 in the L-1210 cell lines in culture was found to be 15x weaker than that of methotrexate. (Author abstract) (30 Refs)

54. PREPARATION AND BIOLOGICAL ACTIVITIES OF 10-DECARBAMOYLOXY-9-DEHYDROMITOMYCIN B AND ITS ANALOGS.

Urakawa C, Tsuchiya H, Nakano KI, Nakamura N
Tokyo Res. Lab., Kyowa Hakko Kogyo Co., Ltd., 3-6-6 Asahimachi, Machidashi, Tokyo 194, Japan
J Antibiot (Tokyo); 34(9):1152-1156 1981

A new naturally occurring mitomycin, 10-decarbamoyloxy-9-dehydromitomycin B, was prepared by treating mitomycin B with sodium hydride. Its analogs having an exo-cyclic double bond in their structure were also synthesized. These compounds showed antibacterial and cytotoxic activities. Among them, 7-amino-10-decarbamoyloxy-9-dehydro-7 demethoxymitomycin B was the most potent growth inhibitor of KB cells in vitro and, accordingly, it appears to be a potential antitumor agent. (Author abstract) (5 Refs)

55. CC-1065 (NSC 298223), A POTENT NEW ANTITUMOR AGENT IMPROVED PRODUCTION AND ISOLATION, CHARACTERIZATION AND ANTITUMOR ACTIVITY.

Martin DG, Biles C, Gerpheide SA, Hanka LJ, Krueger WC, McGovren JP, Mizsak SA, Neil GL, Stewart JC, Visser J
Res. Laboratories, Upjohn Co, Kalamazoo, MI, 49001
J Antibiot (Tokyo); 34(9):1119-1125 1981

CC-1065 (NSC 298223) is a potent new antitumor antibiotic with a unique structure produced by Streptomyces zelensis. Improved production, isolation, and assay methods are described along with physico-chemical properties and antitumor activity. (Author abstract) (7 Refs)

56. EFFECT OF NITIDINE CHLORIDE ON THE LIFE CYCLE OF EHRLICH ASCITES CARCINOMA CELLS IN MICE.

Fan YJ, Zhou J, Li M
Inst. Medical, Pharmaceutical Sci. of Guangni Chuang Autonomous Region, Manning, People's Republic of China
Zhongguo Yaoli Xuebao; 2(1):46-49 1981

Nitidine chloride, an alkaloid isolated from Zanthoxylum nitidum (Roxb) has been shown to have antitumor activities against experimental tumors (eg leukemia L1210 and P388). Using autoradiography, its effect on the cell cycle of Ehrlich ascites carcinoma (EAC) was studied and results are described. The cell cycle time was found to be 38.8 hr. Times for the G1, S, G2 and M periods were 8.0, 25.8, 3.8 and 1.2 hr respectively, with a growth fraction of 0.86. When given ip to EAC-bearing mice, nitidine chloride decreased the mitotic in den and increased the proportion of large-sized EAC cells, indicating a G2 block, but it had no effect on the tritium-TdR pulse labeling index. At 40 mg/kg, nitidine chloride appeared to have killing effects on S cells. It also exhibited significant inhibitory effects on DNA synthesis and lesser effects on RNA synthesis. (7 Refs) (In CHI)

57. EFFECT ON ANIMAL TUMORS AND TOXICITY OF LYCOBETAINE ACETATE.

Zhang SY, Lu F, Yang J, Wang L, Yu B
Sheghai Institute of Metcria, Medica, Chinese Academy of Sciences, Shanghai, People's Republic of China
Zhongguo Yaoli Xuebao; 2(1):41-45 1981

Lycobetaine acetate (AT-1840) is a derivative of lycorine and represents a new type of antitumor drug. The antitumor activities and toxicity of AT-1840 and its structure-activity relationship with related compounds are described. When given ip to tumor-bearing rats and mice, AT-1840 significantly increased their survival times. Tumors on which AT-1840 exhibited activity included Ehrlich ascites tumor, leukemia (LY2110 and P-388), hepatoma. Yoshida sarcoma and Lewis lung carcinoma. Lycorine only exhibited weak or no activity. It appears that the phenolic and betaine groups in AT-1840 have some bearing on its antitumor activities. The acute LD50 of AT-1840 in mice was 72 mg/kg (ip). When given to dogs 3 or 9 mg/kg (iv) every other day for 7 times, AT-1840 produces no significant toxic effects. (6 Refs) (In CHI)

58. CHEMOTHERAPEUTICALLY ACTIVE MAYTANSINOIDS FROM 'TREWIA NUDIFLORA'.

Powell RG, Smith CR

Dept. Agriculture, Washington, DC

Chemotherapeutically Active Maytansinoids from Trewia nudiflora'. Available from National Technical Information Service, Springfield, VA, as PAT-APPL-6-228 853:, 21 pp., 1981.

A novel group of maytansinoid compounds has been discovered in the seed tissue of Trewia nudiflora. They are all characterized by a distinguishing methoxy group on the C-15 carbon. These isolates have proven to be effective in causing the remission of one or more types of malignancies. (Author abstract)

59. THE CROWN-GALL POTATO DISK BIOASSAY AS A PRIMARY SCREEN FOR COMPOUNDS WITH ANTITUMOR ACTIVITY.

Galsky AG, Kozimor R, Piotrowski D, Powell RG

Dept. Biology, Bradley Univ., Peoria, IL, 61625

JNCI; 67(3):689-692 1981

A variety of samples consisting of purified compounds (of various origins) and ethanol extracts from plants were assayed for their activity on the growth and initiation of crown-gall tumors on potato disks. The results demonstrated a high correlation between the ability of these compounds to inhibit the initiation and growth of crown-gall tumors on potato disks and their corresponding activity on the mouse P388 leukemia protocol. Of the 21 compounds tested to date, there were 2 false-positives and 1 false-negative. (Author abstract) (12 Refs)

60. BIOLOGICAL EFFECT OF PLATINUM(II) COMPLEXES WITH TWO DIFFERENT NEUTRAL LIGANDS OF CIS-(PTNH3LCL2) TYPE.

Ivanov VB, Chel'tsov PA, Shchelokov RN

N. S. Kurnakov Inst. General and Inorganic Chemistry, Moscow, USSR

Izv Akad Nauk SSSR [Biol]; (4):551-557 1981

The structure-activity relationship of a series of antitumor platinum(II) compounds was studied in maize seedling roots. All complexes tested were significantly less active than cis-dichlorodiaminoplatinum (II). Only benzylamine-containing complex produced selective inhibition of mitotic activity. (12 Refs) (In RUS)

STUDIES OF ANTIMETASTATIC AGENTS

61. INHIBITION OF LYMPH NODE METASTASIS OF P388 LEUKEMIA BY BESTATIN IN MICE.

Tsuruo T, Naganuma K, Iida H, Yamori T, Tsukagoshi S, Sakurai Y
Cancer Chemotherapy Center, Japanese Foundation for Cancer Res.., Toshima-ku, Tokyo 170, Japan
J Antibiot (Tokyo); 34(9):1206-1209 1981

Bestatin, a chemically defined immunostimulant of low mol wt, suppressed the gradually-occurring lymph node metastasis of P388 leukemia in CDF1 mice when administered ip at the doses of 1 and approx 30 ug/mouse. It could not, however, suppress the established large metastasis of P388 leukemia. Lymph node cells isolated from the mice given bestatin ip at 1 and 30 ug/mouse showed stronger cytostatic activity against P388 leukemic cells in vitro than those from the untreated mice. (Author abstract) (10 Refs)

62. DISULFIDE BONDS PROTECT THE ENCAPSIDATED CHROMOSOMES OF SIMIAN VIRUS 40.

Ng SC, Bina M
Dept. Chemistry, Div. Biochemistry, Purdue Univ., West Lafayette, IN, 47906
FEBS Lett; 130(1):47-49 1981

To study the role of disulfide bridges in the protection of encapsidated simian virus 40 (SV40) DNA, the accessibility of viral DNA to micrococcal nuclease (MN) in the presence or absence of reducing agent dithiothreitol (DTT) was tested. Incubation of SV40 virions with increasing concentrations of MN in 5 milliM (mM) calcium chloride did not result in the cleavage of viral DNA. Incubation of SV40 virions with DTT and subsequent treatment with MN and calcium chloride (greater than 1 mM) resulted in digestion of viral DNA. Calcium chloride was only required for the activation of MN. Fractionation on the isokinetic sucrose gradients showed that the digested particles sedimented similarly to the intact virions. Since SV40 virions do not contain histones H1 or H5, it was concluded that specific types of interactions mediated by divalent ions, protein-protein and protein-DNA prevent the release of nucleosome cores generated by the action of MN on DTT-treated virions. (16 Refs)

63. ENHANCED ANTI-CANCER EFFECT BY COMBINING CYTOTOXIC DRUGS WITH THE PROSTAGLANDIN SYNTHESIS INHIBITOR FLURBIPROFEN.

Bennett A, Berstock DA, Carroll MA
Dept. Surgery, King's Coll. Hosp. Medical Sch., London SE5 8RX, England
Br J Pharmacol; 74(1):208p-209p 1981

Approx 10(6) NC carcinoma cells were injected sc into the left flank of 250 female WHT/Ht mice. Drug treatment by mouth commenced on day 13; primary tumors were excised the next day. Survival was similar in controls and chemotherapy (1.4 mg/kg melphalan, 2 mg/kg methotrexate) groups but longer in mice given 2.5 mg/kg flurbiprofen (F) bid and even long with F + chemotherapy: respectively, 45, 49, 53.5, and 71 days. Mice given F alone or with chemotherapy had a lower incidence of distant metastases than controls, since after 120 days 15 and 16 vs 4 disease-free animals remained. Local recurrence at the excision site was also reduced in the two groups receiving F. F combined with cytotoxic chemotherapy prolongs survival time of mice after excision of primary NC tumors and reduces recurrence at the excision site. (3 Refs)

INTERFERON AND OTHER ANTIVIRALS

64. BIOLOGICAL ACTIVITIES AND MODES OF ACTION OF 9-ALPHA-D-ARABINOFURANOSYLADENINE AND 9-ALPHA-D-ARABINOFURANOSYL-8-AZAADENINE.

Bennett LL, Allan PW, Shaddix SC, Shannon WM, Arnett G, Westbrook L, Drach JC, Reinke CM
Biochemistry Res. Dept., Southern Res. Inst., 2000 Ninth Ave. South, Birmingham, AL, 35255
Biochem Pharmacol; 30(16):2325-2332 1981

From earlier studies it is known that 9-alpha-D-arabinofuranosyladenine (alpha-araA) and 9-alpha-D-arabinofuranosyl-8-azaadenine (alpha-ara-8-azaA) have in vitro antiviral activity, are cytotoxic, and are metabolized in mammalian cells to the triphosphates. This study was designed to compare the in vivo antiviral activities of these compounds and their loci of action with those of 9-beta-D-arabinofuranosyladenine (beta-araA). The latter compound selectively inhibits DNA synthesis in intact cells, and its triphosphate is a known inhibitor of DNA polymerases and ribonucleotide reductase. Whereas beta-araA was significantly effective in the treatment of systemic herpes simplex virus Type 1 (HSV-1) infections in mice, alpha-araA and alpha-ara-8-azaA were therapeutically ineffective. Alpha-AraATP at a concentration of approx 1 mM did not inhibit (1) DNA polymerases present in crude extracts of cultured HEp-2 cells; (2) DNA polymerases present in extracts of KB cells; (3) partially purified DNA polymerase-alpha from mouse embryo cells; or (4) DNA polymerases induced by HSV-1 and HSV-2. DNA polymerase-beta from mouse embryo cells was inhibited to a small extent by 10(-4) M alpha-araATP. In contrast, all of these enzymes were inhibited by beta-araATP at a concentration of 10(-5) M (as shown in these or in earlier studies). The reductions of CDP and UDP by ribonucleotide reductase from L1210 cells were not inhibited by alpha-araATP (approx 10(-3) M), whereas beta-araATP produced 70-80% inhibition at this concentration. In cultured HEp-2 cells, alpha-ara-8-azaA inhibited the incorporation of thymidine, uridine, and formate into macromolecules, but it was without effect on the incorporation of adenine and hypoxanthine, and produced marginal inhibition of the incorporation of leucine. alpha-Ara-8-azaA produced a dose-dependent inhibition of the accumulation of [14C]formyl-glycinamide ribonucleotide in HEp-2 cells treated with azaserine and [14C]formate. These results indicate that the alpha-nucleosides inhibit nucleic acid synthesis by mechanisms different from those of beta-ara-A. (Author abstract) (32 Refs)

65. INTERFERON: INDUCTION, PRODUCTION AND PHYSICOCHEMICAL PROPERTIES (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Interferon: Induction, Production and Physicochemical Properties (Oncology Overview) Marcus, P I, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923003:; 0B-81/03:77pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. The scope of this Oncology Overview includes the induction and superinduction of interferon in human animal cells. Interferon production in vivo and in vitro, factors enhancing or inhibiting interferon production, and the priming of interferon production by interferon are covered. The purification and physicochemical properties of interferons are also considered. However, the many actions of interferon and interferon inducers are not covered here, as these topics will appear in separate volumes.

66. MECHANISM OF STIMULATION OF NATURAL KILLER-CELL CYTOTOXICITY BY INTERFERON AND AN INTERFERON-INDUCER IN THE RAT.

Flexman JP, Shellam GR
Dept. Microbiology, Univ. Western Australia, Queen Elizabeth II Medical Centre, Nedlands, Western Australia 6009, Australia
Immunology; 44(2):311-320 1981

The interferon-inducer Newcastle disease virus (NDV) was shown to augment cytotoxicity attributable to natural killer (NK) cells in all of the major lymphoid organs of W/Fu rats except the thymus. The levels of interferon isolated from the spleen following NDV inoculation correlated with the increase in splenic cytotoxicity from the same spleen. Spleen-derived interferon was shown to augment splenic cytotoxicity following iv inoculation, and to augment spleen cell cytotoxicity in vitro. Three major peaks of interferon Type I were found in spleen homogenates corresponding to mol wt of greater than 100,000, 29-33,000 and 19-23,000. All these fractions stimulated spleen cell cytotoxicity when tested in vitro. The rapid drop in splenic cytotoxicity 24 hr after NDV inoculation was associated with a rapid fall in interferon levels in vivo. The need for the continued presence of interferon for the stimulation of cytotoxicity was demonstrated when spleen cells pretreated with interferon for 4 hr in vitro lost their augmented cytotoxicity upon culturing for a further 20 hr in the absence of interferon. Although splenic cytotoxicity returned to control levels within 24 hr of a single 107.3 EID50 dose of NDV, repeated doses of NDV maintained augmented cytotoxicity over a longer period. Spleen cells either taken from rats injected with NDV or pretreated in vitro with interferon showed a two-fold increase in the number of cytotoxic cells bound to W/FuG-1 target cells, with no change in the target binding-cell numbers. However, only the cells pretreated with interferon showed an increase in lytic efficiency. (Author abstract) (30 Refs)

67. PHARMACOKINETIC STUDIES OF INTERFERONS.

Bocci V
Inst. General Physiology, Univ. Siena, 53100 Siena, Italy
Pharmacol Ther; 13(3):421-440 1981

The behavior of the various types of interferon (IF) from human sources in the human body in consequence of dilution, cell binding, and catabolism is reviewed. General considerations of the metabolism of IFs are discussed, including the need for homogeneous IF and a radioimmunoassay for IF, and problems with the rapid metabolism of IF. The question of whether IF binding to the cell receptor represents a first catabolic step is addressed, as are the catabolic roles of the liver, kidney and muscle; the metabolic role of the endothelial cells; whether any IF leaks into the gastrointestinal lumen, whether the lung has any catabolic role; and the role of neutrophils and mononuclear phagocytes. An attempt was made to present a conceptual framework to be used for future pharmacokinetic studies. It appears that the most sialylated IF, particularly without any exposed galactose, should be the least susceptible to hepatic uptake and renal filtration. Further studies should be directed at defining the factors controlling distribution, uptake or metabolism of IF so that it can be applied more readily and successfully in human and veterinary medicine. (200 Refs)

68. ANTITUMOR AND RADIATION SENSITIZING EFFECTS OF HUMAN LEUKOCYTE INTERFERON IN VITRO.

Ito H
Dept. Radiology, Kyoto Prefectural Univ. Medicine, Kyoto, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(6):551-558 1981

The antitumor and radiation sensitizing effects of interferon (IF) on human fibroblasts and KB cells were studied in vitro. Both types of the cells were irradiated by 60Co-gamma-rays. When the fibroblast was cultured with IF preparation, IF preparation did not suppress its growth; but the growth of the KB cell was suppressed by IF treatment. When the fibroblast was irradiated together with IF treatment (pretreated and posttreated), no effect was detected on its growth. When the KB cell was irradiated together with IF preparation, only posttreatment with IF preparation affected its growth. Further more, the KB cell was studied by the colony formation method. The radiation effect was enhanced by treatment with IF preparation. (Author abstract) (18 Refs) (In JPN)

69. PERSISTENT REACTIVABLE LATENT HERPES SIMPLEX VIRUS INFECTION IN TRIGEMINAL GANGLIA OF MICE TREATED WITH ANTIVIRAL DRUGS.

Svennerholm B, Vahlne A, Lycke E
(c/o Lycke) Dept. Virology, Inst. Medical Microbiology, Guldhedsgatan 10B, S-413 46 Goteborg, Sweden
Arch Virol; 69(1):43-48 1981

Latent reactivable infection was established with HSV in mouse trigeminal ganglion. A number of antiviral drugs (IUDR, acycloguanosine, Ara-A, PAA and PFA), effective against acute CNS infection with HSV, failed to influence the latent infection once established. Neither lipophilic properties of PFA-derivatives nor the combination of Ara-A and acyloguanosine improved the drug-effects on HSV latency. (Author abstract) (19 Refs)

OTHER RELATED STUDIES

70. POSSIBILITIES AND PROBLEMS OF ORGAN-SELECTIVE AGENTS AND DRUGS.

Hamacher H
Konigin-Luise Str. 2-4, D-1000 Berlin, W. Germany
Pharmazie; 36(6):391-399 1981

The development of organ-selective methods of treatment are reviewed, and several specific types of treatment are described. Localized therapy involves the introduction of an agent into the site to be treated. An example of this is the progesterone intrauterine contraceptive system. A second method relies on the differences between metabolic processes in normal and malignant cells. Compounds such as cyclophosphamides are used to selectively poison tumor cells. Acid-stimulating compounds can lower the pH of tumor cells, allowing cytotoxic agent active at lower pH to be effective. Liposomes, in which water-soluble compounds are enveloped in lipid double-layers, enable the transport of agents selectively into target cells. Micelles work in a similar manner. Certain radioactive elements have been shown to accumulate selectively in certain organs, such as 131I in the thyroid. This has provided diagnostic and therapeutic tools, useful particularly in malignant diseases. The combining of isotopes with specific carrier compounds allows the specific targeting of organs or tissues. Hormones with specific organ affinities, as well as specific hormone receptors, can also be used to direct cytotoxic agents at specific targets. The development of organ-specific treatments has many possibilities for treatment of cancer and other diseases. (52 Refs) (In GER)

71. MALEIC VINYL ETHER ACTIVATION OF MURINE MACROPHAGES AGAINST LUNG-METASTASIZING TUMORS.

Loveless SE, Munson AE
Dept. Immunology, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201
Cancer Res; 41(10):3901-3906 1981

A.M.W. 15,500 fraction of maleic vinyl ether (MVE-2) induced tumoristatic and tumoricidal activity in peritoneal macrophages of BALB/c and C57BL/6 mice following ip administration. Growth of B16 melanoma cells in vitro was inhibited up to 85% by MVE-2-activated, but not resident, peritoneal macrophages. In a tritiated thymidine release assay, B16 melanoma cells, and to a lesser extent Madison 109 lung carcinoma cells, were also sensitive to the cytolytic action of MVE-2-activated peritoneal macrophages. Administration iv of MVE-2 resulted in tumoristatic and tumoricidal activity in alveolar macrophages against radiolabeled B16 and Madison 109 lung carcinoma target cells. MVE-2-activated alveolar macrophages significantly inhibited L5178Y lymphoma colony formation following a 48-hr macrophage-tumor coincubation. BALB/c mice bearing the lung-metastasizing Madison 109 lung carcinoma footpad tumor were given MVE-2 iv, using the same dosing regimen that induced alveolar macrophages to be tumoricidal in vitro. Significant increase in life span were observed, suggesting that the antitumor activity of MVE-2 in this tumor system may be mediated by the activation of alveolar macrophages, with a resulting decrease in metastatic growth in the lung. (Author abstract) (30 Refs)

72. IN VIVO INHIBITION OF THE DEVELOPMENT OF MYELOID LEUKEMIA BY INJECTION OF MACROPHAGE- AND GRANULOCYTE-INDUCING PROTEIN.

Lotem J, Sachs L
Dept. Genetics, Weizmann Inst. Science, Rehovoth 76100, Israel
Int J Cancer; 28(3):375-386 1981

Injection of macrophage- and granulocyte-inducing protein (MGI) can inhibit the development of myeloid leukemia in vivo and stimulate normal myelopoiesis. The MGI injected contained MGI-I activity that induces colony formation with normal myeloblasts, and MGI-2 activity that induces differentiation of normal and MGI 7+ 1D 7+ 1 leukemic myeloblasts to mature macrophages or granulocytes. Injection of MGI reduced the tumor vol in mice sc inoculated with leukemic cells at least 50-fold The median survival time of MGI 7+ 1D 7+ 1 cells or sc with MGI 7+ 1D 7-1 cells was increased by about 40%, and 50% of the MGI-treated mice inoculated sc with MGI 7+ 1D 7+ 1 cells did not develop tumors. MGI also increased the anti-tumor effect of cyclophosphamide. The leukemia-inhibiting activity in the injected MGI preparations was associated with the peak of MGI activity separated on a hydroxylapatite column and was destroyed by treatment at the temperature which destroys MGI-2 activity. This indicates that the inhibition of leukemia development was mediated by MGI-2. It is suggested that improved schedules of MGI treatment, with or without compounds used in the cytotoxic types of therapy, should be able to give an even better inhibition of leukemia development and that these results should also be applicable to the therapy of human myeloid leukemia. (61 Refs)

73. DRUG SENSITIVITY AND SOME CHARACTERISTICS OF A BLEOMYCIN-RESISTANT SUBLINE OF MO USE LYMPHOBLASTOMA L5178Y CELLS.

Suzuki H, Nishimura T, Tanaka N
Inst. Applied Microbiology, Univ. Tokyo, Tokyo, Japan
J Antibiot (Tokyo); 34(9):1210-1212 1981

A bleomycin (BL)-resistant subline of mouse lymphoblastoma L5178Y clls was isolated by the repeated injection of bleomycin A2 (BL-A: 10 mg/kg) in tumor-bearing CDFl female mice. The resistant cells grew more slowly than the parental cells; and the 50% inhibitory concentration (IC50) of BL-A on culture day 3 was 3.2 ug/ml for the resistant cells, vs 0.28 ug/ml for the parental cells. The IC50 for DNA-binding antibiotics (eg, adriamycin, neocarzinostatin, macromomycin, mitomycin C, aclacinomycin A) were similar for the resistant and parental cells; thus, these drugs showed no cross resistance with BL in the resistant cells. In contrast, cross resistance was observed with peplomycin. Measurements of BL-inactivating enzyme levels in the parental and subline cells showed that the resistance was not due to increased enzyme activity. The possibility that the resistance is due to plasma membrane alterations is discussed. (6 Refs)

74. ALTERATION OF BLOOD-CSF BARRIER BY TUMOR INVASION INTO THE MENINGES.

Ushio Y, Shimizu K, Aragaki Y, Arita N, Hayakawa T, Mogami H
Dept. Neurosurgery, Osaka Univ. Medical Sch., 1-1-50, Fukushima, Fukushima-ku, Osaka 553, Japan
J Neurosurg; 55(3):445-449 1981

Cyclophosphamide and 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2 chloroethyl)-3-nitrosourea hydrochloride (ACNU) were found to have an equivalent cytostatic effect in rats with sc transplants of Walker 256 carcinosarcoma. Rats with meningeal carcinomatosis received a single iv dose of cyclophosphamide (30 mg/kg) or ACNU (15 mg/kg) at various times after intracisternal inoculation of 1 x 10(4) Walker 256 carcinosarcoma cells. Cyclophosphamide, administered 1 day after tumor inoculation, failed to prevent tumor growth in the subarachnoid space. The survival time of these rats was prolonged only 10% to 14% compared to the controls, while ACNU produced a max increased survival time of 180%. If administered 2, 3, 4, and 5 days after tumor inoculation, both drugs were effective; cyclophosphamide yielded a max increase in median survival time of 109%, 94%, 90%, and 52%, and ACNU 127%, 139%, 240%, and 100%, respectively. These results indicate that the blood-cerebrospinal fluid barrier was circumvented in the early stage of subarachnoid tumor growth, although some areas remained where the infiltrating tumor cells were protected from systemically administered drugs by the intact barrier. (Author abstract) (9 Refs)

75. MEASUREMENT OF DAUNORUBICIN UPTAKE OF YOSHIDA SARCOMA CELLS IN CULTURE USING FLOW CYTOFLUORIMETRY.

Garner A, Fox BW
Dept. Biochemistry, Brunel Univ., Uxbridge, Middlesex, England
Chem Biol Interact; 35(2):189-210 1981

A comparative measurement of the transport and localization of daunorubicin into Yoshida sarcoma cells, was undertaken by a biochemical extraction process and a flow cytometric method. An advantage of this latter procedure would be to identify subpopulations of cells which have enhanced or impaired daunorubicin incorporation as well as the ability to exclude any non-specific incorporation into cell debris, which would otherwise interfere with the overall estimation. It has been possible to use the Biophysics argon ion laser at a wavelength of 488 nm which coincides with the visible absorption bands of daunorubicin and doxorubicin (adriamycin) and the cytofluorimetric estimations of daunorubicin incorporation have now been compared with biochemically determined uptake in Yoshida cells. A high lethal dose of 10 uM was required to achieve the direct measurement by cytofluorimetry procedures on the Biophysics instrument. From cell fractionation and CHCl3/amyl alcohol extraction, it was possible to show that during a 5-hr exposure period to daunorubicin (10 uM), the uptake into the nucleus was at first rapid and that into the cytoplasm was much slower. After about 3-hr incubation, the level in the cytoplasm decreased, followed by a decrease from the nucleus 1 hr later. This could be equated when observed microscopically to the gain in fluorescent cell debris. If all nuclear binding is to DNA, then at the level of (10 uM) concentration in the medium, the number of base pairs to daunorubicin would be 9:1, respectively. Cytofluorimetry showed a broad spread of intracellular daunorubicin fluorescence which increases with cell size. Increasing external concentration caused a more rapid incorporation as well as a quicker release from the cells. (Author abstract) (36 Refs)

76. THE EFFECTS OF SOME PHYSICAL FACTORS ON THE PRODUCTION OF HYPERTHERMIA BY ULTRASOUND IN NEOPLASTIC TISSUES.

Hynynen K, Watmough DJ, Mallard JR
Dept. Bio-Medical Physics and Bio-Engineering, Univ. Aberdeen, Foresterhill, Aberdeen AB9 2ZD, Scotland
Radiat Environ Biophys; 19(3):215-226 1981

A one-dimensional and a three-dimensional computer model were built to study the relative importance of blood flow, thermal conduction, and ultrasonic absorption in tumors and surrounding tissue during local hyperthermia. The model is based on the bio-heat transport equation; data for temperature distribution calculations were collected from the literature. The 1-30% decreased blood flow in tumors relative to surrounding tissue is sufficient to cause therapeutically useful temperature increase in tumor if the heat input is equal in both tissues. When the temperature of the surrounding liver is approx 40.5 C after 20 min heating, the temperature in a hypothetical 2 cm tumor is 41.5, 42.5, 44.5, and 48 C if blood flow in the tumor is respectively 75, 50, 25, and 0% of that in the liver. The higher absorption of ultrasound in malignant tissues may cause similar advantage, as does temperature-stabilizing vasodilation above 42 C in healthy tissue. Inhomogeneity of tumor blood flow means that the necrotic center is easy to heat but the well-perfused advancing front requires much higher and selective heat input to reach the same temperature. Under similar conditions, small tumor temperature remains lower than that in large tumors, due to differences in thermal conduction. The combination of local hyperthermia with radio- and chemotherapy offers the most attractive means of destroying malignant tissue. (42 Refs)

77. EXPERIMENTAL INTRA-ARTERIAL INFUSION OF MICROENCAPSULATED MITOMYCIN C INTO PELVIC ORGANS.

Nemoto R, Kato T
Dept. Urology, Akita Univ. Sch. Medicine, 010 Akita, Japan
Br J Urol; 53(3):225-227 1981

Laboratory experience with the use of mitomycin C (MMC) encased in ethylcellulose microcapsules as an agent for transcatheter embolization is described. Microencapsulated MMC (MMC-mc) was infused into the pelvic organs of dogs by arterial catheterization and the distribution of MMC in plasma and tissue was examined. MMC levels in the circulating blood of the MMC-mc group were significantly lower than those of the nonencapsulated MMC group. The biological potential of MMC was retained for prolonged periods in the pelvic organs after ia infusion of MMC-mc. On the other hand, MMC could not be detected in the tissue of the nonencapsulated MMC group 4 hr after the infusion. (Author abstract) (6 Refs)

78. GROWTH RATE OF HUMAN MALIGNANT TUMORS IN NUDE MICE WITH DIFFERENT GENETIC BACKGROUNDS: SELECTION OF STRAINS OF NUDE MICE FOR SCREENING OF ANTITUMOR AGENTS.

Maruo K, Ueyama Y, Hioki K, Saito M, Nomura T, Tamaoki N
Central Inst. Experimental Animals, Takatsu-ku, Kawasaski-shi, Kanagawa Pref. 211, Japan
Igaku No Ayumi; 116(10):825-827 1981

Into 90 male and female nude mice (6-to 8-wk old) of seven different strains, that had been reared under specific pathogen-free conditions, 1 x 10(6) cells of a human gastric cancer (poorly differentiated adenocarcinoma) that had been serially maintained for 25-34 generations sc in BALB/cA-nu mice were transplanted sc. The mice were killed 5 wk later, and the wt of the tumor and type of tumor tissue were determined. The tumors were successfully transplanted into all the CBA/N-nu, NFS/N-nu, NIH(s)-nu and C3H/HeN+-nu mice, but not into 11%, 40% and 25% of the BALB/cA-nu, C57BL/6N-nu and lasat mice, respectively. The av tumor wt for the CBA/N-nu mice was the highest followed by NFS/N-nu, NIH(s)-nu, C3H/HeN+-nu, BALB/cA-nu, lasat and C57BL/6N-nu mice in that order. The av tumor wt for the CBA/N-nu and NFS/N-nu mice was, respectively, 3.5 and 3x that for the BALB/cA-nu mice which are presently used most commonly. Tumors were not successfully transplanted into some of the mice in the group with a low av tumor wt. The difference in tumor wt between BALB/cA-nu and CBA/N-nu or C3H/HeN+-nu mice was statistically significant when analyzed by the t test. Similar results were obtained when human malignant lymphoma and human chronic myeloid leukemia cells were transplanted. Since tumor transplantability into NFS/N-nu and CBA/N-nu mice was high, and the growth of the tumor was rapid and relatively even, these mice are considered to be useful experimental animals. (10 Refs) (In JPN)

79. MURINE MACROPHAGE CYTOTOXICITY INDUCED BY MASTOCYTOMA CELLS, CELL-FREE MASTOCYTOMA EXUDATES, AND EXTRACTS.

Dullens HF, Den Otter W
Dept. Pathology, Utrecht Univ., Pasteurstraat 2, 3511 HX Utrecht, The Netherlands
Immunopharmacology; 3(3):241-251 1981

The induction of macrophage cytotoxicity against nonrelated tumor target cells when the test and target cells were incubated with mastocytoma P815 ascitic fluid and or P815 cell extracts was examined using BALB/c, CBA, C57BL/10, and DBA/2 male and female mice as sources of peritoneal macrophages and cells from the following tumors: SL2, L5178Y, and EL4 lymphosarcomas; TLX9 thymoma; and P815 mastocytoma. CBA macrophages expressed significant cytotoxicity against DBA/2-derived P815 mastocytoma cells but not against DBA/2-derived SL2 cells or against C57BL/10-derived TLX9 or EL4 cells. The CBA macrophages also expressed some cytotoxicity against the DBA/2-derived L5178Y cells. When CBA macrophages were incubated with ip-grown P815 cell-free exudate, cytotoxicity against SL2 and EL4 cells was observed. When SL2 cells were incubated with P815 ascitic fluid before the tumor cells were added to monolayers of CBA macrophages, SL2 cell growth on these monolayers was inhibited. Two treatments were capable of abolishing macrophage cytotoxicity: incubation with ascitic fluid or with tumor extract, followed in either case by trypsinization and then challenge with tumor cells. Trypsinization alone did not effect this loss of activity. Cytotoxicity remained inducible after 7 days' storage of the exudate at-5 C, but was lost after 72 hr of storage at room temperature; storage at-20 C had no effect. The effect is due to a small-mol wt, dialyzable factor of mol wt less than 1,000, according to the results of gel filtration of the cell-free exudate. This factor was not demonstrated in the supernatant of P815 cells unless the cultures contained 40% or more dead cells. Further characterization of the factor and its possible application in therapeutics are under way. (23 Refs)

80. DRUG TARGETING: MAGNETICALLY RESPONSIVE ALBUMIN MICROSPHERES--A REVIEW OF THE SYSTEM TO DATE.

Senyei AE, Widder KJ
Dept. Obstetrics and Gynecology, Univ. California, Irvine Medical Center, Orange, CA, 92668
Gynecol Oncol; 12(1):1-13 1981

Magnetically responsive drug-bearing microspheres fulfill all of the desired properties of an ideal drug carrier. Intra-arterial routes of therapy have shown encouraging results. The present system allows for retention of injected drug at the target site. Gynecologic cancers that are often staged at laparotomy may be very amenable to this form of therapy. It is hoped that the encouraging results obtained to date in small animals will soon lead to human applications. (Author abstract) (15 Refs)

81. HEMATOPOIETIC DISORDERS RESULTING FROM CYTOSTATIC TREATMENT.

Klener P
II. interni klinika, Fakultni nemocnice I s poliklinikou KUNZ SKNV, U nemocnice 2, 128 08 Prague 2, Czechoslovakia
Cas Lek Cesk; 120(25):769-773 1981

Hematopoietic disorders due to cytostatic treatment are reviewed. Impaired hematopoiesis is one of most frequent side-effects of antitumor chemotherapy as an inherent result of nonselective inhibition of proliferating cells. Such drugs as bleomycin, dacarbazine, L-asparaginase, and cis-platinum have only a slight effect on both proliferating and resting hemopoietic cells, while folic acid antagonists (methotrexate), mercaptopurine, cytosine arabinoside, vinca alkaloids (vinblastine and vincristine), and hydroxyurea have a much stronger effect on proliferating than on resting hemopoietic cells. Busulfan, nitrogen mustard, and trichloromethine have noticeable effects on both cell lines, but affect resting cells more strongly than proliferating ones, while cyclophosphamide and adriamycin affect proliferating cells more strongly than resting ones. Nitrosoureas (carmustine and lomustine) affect proliferating and resting cell equally strongly. Transfusion of blood or leukocyte concentrate, corticoid or lithium carbonate treatment are available for the treatment of granulocytopenia induced by cytostatics. Substitution treatment or drug stimulation is indicated for the treatment of thrombocytopenia. Androgens (testosterone) are effective in the treatment of anemia. (18 Refs) (In CZE)

82. COMBINED RADIATION-PROTECTIVE AND RADIATION-SENSITIZING AGENTS. II. RADIOSENSITIVITY OF HYPOXIC OR AEROBIC CHINESE HAMSTER FIBROBLASTS IN THE PRESENCE OF CYSTEAMINE AND MISONIDAZOLE: IMPLICATIONS FOR THE 'OXYGEN EFFECT' (WITH APPENDIX ON CALCULATION OF DOSE-MODIFYING FACTORS).

Koch CJ, Howell RL
Cross Cancer Inst., 11560 University Ave., Edmonton, Alberta T6G 1Z2, Canada
Radiat Res; 87(2):265-283 1981

The radiation sensitivity of both hypoxic and aerobic cells exposed simultaneously to radiation-protector cysteamine (CS) and radiation-sensitizing agent misonidazole (MD) was studied in a culture of V79 Chinese hamster fibroblasts. MD at 2.5 milliM (mM) was found to sensitize hypoxic V79 cells to radiation by a factor of 2.1. Addition of CS to hypoxic cells containing MD provided protection against the radiosensitization by MD at concentrations as low as 0.1 mM. In aerobic cells, protection was achieved at CS concentration of greater than 1 mM of CS; at CS concentration of 30 mM, aerobic cells were as resistant as hypoxic cells without drug but still not as resistant as hypoxic cells with 30 mM of CS. These findings indicate that addition of CS cancels the benefit of MD and thus increases the differential response of hypoxic and aerobic cells. (48 Refs)

83. PHORBOL ESTER DRAMATICALLY INCREASES INCIDENCE OF METHOTREXATE-RESISTANT MOUSE CELLS: POSSIBLE MECHANISMS AND RELEVANCE TO TUMOR PROMOTION.

Varshavsky A
Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cell; 25(2):561-572 1981

I have tested the hypothesis that at least some of the unknown tumor promoters may act by facilitating gene amplification. A series of single-step selections for resistance to methotrexate, a specific inhibitor of dihydrofolate reductase (DHFR), was carried out with 3T6 cells in the presence and in the absence of a potential tumor promoter, 12-O-tetradecanoyl-phorbol-13-acetate (TPA). Incidence of methotrexate-resistant, colony-forming 3T6 cells is increased up to 100 fold if selection is carried out in the presence of TPA. For a major portion of this new TPA effect to be observed, it is sufficient to add TPA simultaneously with methotrexate. The effect of TPA on the incidence of methotrexate resistance is detectable at less than 20 nM TPA and is max at about 200 nM TPA. Phorbol (a non-promoting analog of TPA), thymidine and dimethylsulfoxide each fail to produce any TPA-like effect in this system. DHFR gene copy numbers per cell in clones resistant to 100, 200 and 300 nM methotrexate are approx 3, 10 and 16x higher, respectively, than the DHFR gene copy number in the parental 3T6 cells. These numbers do not depend on the presence or absence of TPA during methotrexate selection. (Author abstract) (37 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

ANTITUMOR AGENT EFFICACY IN VIVO

1. COMBINED EFFECTS OF NATURAL RESISTANCE AND CHEMOTHERAPY AGAINST A MURINE LYMPHOMA IN LETHALLY-IRRADIATED MICE.

Iorio AM, Neri M, Enrico P, Goldin A, Bonmassar E
Chair Virology, Univ. Perugia, Via del Giochetto, Perugia 06100, Italy
Int J Cancer; 28(4):497-502 1981

Lymphoma EL-4 of B6 origin was inoculated into lethally-irradiated syngeneic B6 or resistant BD2F1 hybrid recipients. Marked impairment of lymphoma cell proliferation (ie hybrid resistance, HR) occurred in the spleen but not in the liver or lung of BD2F1 hosts. Treatment with DTIC at the optimal dose of 80 mg/kg ip produced inhibitory effects in spleen, liver and lung of young BD2F1 mice, that were much greater than those observed in syngeneic B6 hosts. Increased anti-lymphoma effects for HR and DTIC chemotherapy were not detectable in the liver or lung of old BD2F1 mice or in the spleen, liver or lung of young hybrid recipients depressed for HR by pretreatment with cyclophosphamide. This is the first report on combined anti-leukemic effects of the host's antitumor natural resistance and chemotherapy. (Author abstract) (36 Refs)

2. TREATMENT OF MALIGNANT MELANOMA BY INTRAVASCULAR 4-HYDROXYANISOLE.

Morgan BD, O'Neill T, Dewey DL, Galpine AR, Riley PA
Univ. Coll. Hosp., Gower St., London WCI, England
Clin Oncol; 7(3):227-234 1981

Regression of localized malignant melanomas treated by ia infusion of 4-hydroxyanisole (4-OHA) is reported. No generalized toxic effects of 4-OHA were observed. Iv administration of the drug was not therapeutically effective. (Author abstract) (13 Refs)

ANTITUMOR AGENT EFFICACY IN VITRO

3. INDUCTION OF DIFFERENTIATION OF HUMAN PROMYELOCYTIC LEUKEMIA CELLS (HL-60) BY NUCLEOSIDES AND METHOTREXATE.

Bodner AJ, Ting RC, Gallo RC
(c/o Ting), Biotech Res. Lab., 3 Taft Court, Rockville, MD, 20850
JNCI; 67(5):1025-1030 1981

Various purine and pyrimidine analogs and methotrexate were tested to determine whether they induce morphologic and functional myeloid differentiation in HL-60, a human promyelocytic leukemia cell line. Functional maturity was assessed by nitro blue tetrazolium reduction assays. 3-Deazauridine caused nearly all of the cells to differentiate during 6 days of treatment. Pyrazofurin, virazole, puromycin aminonucleoside, and the tricyclic nucleoside 3-amino-1,5-dihydro-5-methyl-1-beta-D-ribofuranosyl 1,4,5, 6,8-pentaazaacenaphthylene induced maturation in 44-64% of the cells, whereas 5-azacytidine, 5-bromo-2'-deoxyuridine, 5-iodo-2'-deoxyuridine, thymidine, and the antimetabolite methotrexate induced maturation in 28-36% of the cells. In terms of effective concentration, the most potent inducer was methotrexate (10(-8) M). The predominant cell types after treatment with all of these compounds were the metamyelocyte and banded neutrophilic granulocyte. (Author abstract) (34 Refs)

4. THE EFFECT OF LOW-MOLECULAR-WEIGHT INHIBITORS ON THE GROWTH IN VITRO OF A HUMAN PANCREATIC ADENOCARCINOMA CELL LINE.

Grant AG, Grant DA
Dept. Surgery, St. George's Hosp. Medical Sch., Cranmer Terrace, London SW17 0RE, England
Biochem Soc Trans; 9(1):134 1981

Inhibition of growth in an in vitro human pancreatic exocrine adenocarcinoma cell line was studied. Low mol wt proteinase inhibitors included antipain and leupeptin (active against trypsin -like enzymes), pepstatin (active against pepsin-like enzymes), and elastatinal (active against elastase-like enzymes). Growth was decreased 50% by 5-25 uM leupeptin or antipain. Cell numbers were reduced by 50 uM leupeptin to 35% and by 50 uM antipain to 25% of control values. Pepstatin and elastinal had no effect. [3H]-thymidine labeling occurred in 63% of controls within 24 hr. Doubling time was delayed 24 hr by 5 uM leupeptin. Antipain (5 uM) had no effect on cell division rate, but decreased the number of cells reaching interphase. Reseeding of cells in medium without inhibitors resulted in return to normal growth rate, suggesting that the inhibition was reversible. No cell toxicity was noted for 5-25 uM antipain or leupeptin. In tests to quantify the amount of inhibitor in culture medium by measuring inhibition of trypsin activity in cell-free medium, trypsin hydrolysis was reduced to a constant value regardless of whether the medium was assayed before, during, or after growth studies. This indicated that the inhibitors were not taken up by cells, but acted extracellularly. Results suggest that in vivo use of proteinase inhibitors for treatment of tumors would require long-term administration. (6 Refs)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

5. ENHANCEMENT OF METHOTREXATE ACTIVITY BY THEOPHYLLINE IN HELA CELL CULTURES (41241).

Bendas CM, D'Antonio LE
Dept. Microbiology, Philadelphia Coll. Osteopathic Medicine, Philadelphia, PA, 19131
Proc Soc Exp Biol Med; 168(1):105-109 1981

The ability of 1.0 milliM theophylline (TP) to enhance methotrexate (MTX: 0.5 ug) activity in cultured HeLa cells (JJH strain) was examined. A series of experiments were performed to determine if the observed reduction in cellular growth rate was due to TP toxicity. Viable and total cells counts were done on the HeLa cell cultures in the log phase of growth. No significant difference in viability was observed between cells grown in 1.0 milliM TP and those grown in growth medium alone. These results confirmed that the addition of TP to the medium of cultured cells slowed the growth rate without adversely affecting cellular viability. Untreated HeLa cells increased at a rate of 2.9 x 10(5) cells/day as compared to an increase of 1.4 x 10(5) cells/day for TP-treated cells. The cultures receiving MTX alone lost 2.9 x 10(4) cells/day while the cells receiving the combination of TP and MTX lost 7.4 x 10(4) cells/day. The rate of cell loss in cultures treated with combined TP and MTX was over 2.5 times greater than the loss of viable cells in cultures receiving MTX alone. TP enhanced the growth-inhibiting activity of even low-dose (0.1 ug/ml) MTX. (15 Refs)

6. RESPONSE OF 9L RAT BRAIN TUMOR TO COMBINATION TREATMENT WITH RADIATION AND BLEOMYCIN.

Kimler BF, Vats TS, Lorantz RA, Henderson SD
Radiation Biology Lab., Dept. Radiation Therapy, Univ. Kansas Medical Center, Kansas City, KS, 66103
Int J Radiat Oncol Biol Phys; 7(8):1069-1074 1981

The interaction of radiation therapy and bleomycin (BLM) was studied in male Fischer 344 rats with intracerebral 9L gliosarcomas. Increased median survival time (MST) was observed in tumor-burdened rats treated with either a low-dose radiation therapy schedule (15.3 Gray: Gy, in 6 equal fractions over 2 wk), a high-dose radiation therapy schedule (30.6 Gy by the same schedule), or the low-dose schedule in combination with BLM (1.0 mg/kg/wk) delivered intracerebrally. BLM was effective whether given simultaneously or following fractionated radiation therapy. The greatest enhancement in survival caused by combination therapy compared to that by single agent therapy was observed when single exposure radiation therapy (20 Gy) followed single BLM administration by 4 hr. The results indicated that BLM used in combination with radiotherapy may be useful in the treatment human brain neoplasms. (16 Refs)

7. BRAIN TUMOR THERAPY: PROSPECTS FOR COMBINING BCNU WITH CONVENTIONAL RADIOTHERAPY SCHEDULES.

Wheeler KT, Kaufman K
Cancer Center, Univ. Rochester, Box 704, 601 Elmwood Ave., Rochester, NY, 14642
Int J Radiat Oncol Biol Phys; 7(8):1065-1068 1981

The effectiveness of 1,3-bis(2-chloroethyl)-1 nitrosourea (BCNU) given 2x (3.0 mg/kg) or 3x (2.5 mg/kg) per wk during a conventional daily fractionated radiotherapy schedule (260 rad fractions/wk) were compared with the best daily combination schedule of BCNU (2.0 mg/kg) and radiation for the treatment of male Fischer 344 rats bearing intracerebral 9L/Rn tumors. The median day of death of untreated tumor-bearing rats was 16. Neither x-rays alone nor any of the BCNU alone schedules significantly increased the life span of tumor-bearing rats over that of untreated controls. All three combination schedules significantly increased the lifespan of tumor bearing rats over that observed for untreated tumor-bearing rats and those treated with any schedule of the single agents. Although the combination schedules in which BCNU was administered either 2-3x per wk during daily unfractionated radiotherapy were equally effective (p less than 0.05) in increasing the lifespan of tumor-bearing rats, neither was as effective (p less than 0.04) as the combination schedule in which daily fractions of BCNU were administered during radiotherapy. (16 Refs)

8. EFFECT OF CIS-DICHLORODIAMMINE PLATINUM II AND X RAYS ON MAMMALIAN CELL SURVIVAL.

Carde P, Laval F
(c/o Laval), Institut de Recherches de Radiobiologie Clinique (INSERM), 94800 Villejuif, France
Int J Radiat Oncol Biol Phys; 7(7):929-933 1981

The influence of cis-dichlorodiammine platinum II (cis-Pt (II)) on the survival of x-irradiated H4 cells derived from a rat hepatoma was studied in an attempt to determine the potential use of this drug to increase the efficiency of radiotherapy. In studies of cis-Pt (II) cytotoxicity, it was found that plateau phase cells were less sensitive to the drug than were exponential cells. When plateau phase cells were incubated for 1 hr with cis-Pt (II) and then irradiated, the survival curves showed modifications both of the extrapolation number and the slope of the curve. The Do decreased from 140 rad for control cells to 135 rad for the cis-Pt (II)-treated cells. Cis-Pt (II) had the same toxicity in both euoxic and hypoxic plateau H4 cells. However, the decrease in Do was more pronounced when plateau cells were treated with cis-Pt (II). The effects of the cis-Pt (II) on the survival curve and Do of exponentially growing H4 cells were insignificant. The repair of sublethal damage (SLD) was measured in exponentially growing H4 cells treated or not treated with cis-Pt (II). Cis-Pt (II) was found to inhibit the repair of SLD. This inhibition was observed only when the drug was present in the medium during the fractionation period. When plateau phase cells were irradiated with 750 rad and then incubated with cis-Pt (II), the survival increase, observed in control cultures, was no longer evident. The results suggested that combined treatment with cis-Pt (II) and ionizing radiations could increase the efficiency of radiation, especially in the case of stationary cells in hypoxia. (20 Refs)

9. POTENTIATION OF THE ANTITUMOR THERAPEUTIC EFFECTS OF 1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA BY ALPHA-DIFLUOROMETHYLORNITHINE, AN ORNITHINE DECARBOXYLASE INHIBITOR.

Marton LJ, Levin VA, Hervatin SJ, Koch-Weser J, McCann PP, Sjoerdsma A
Dept. Lab. Medicine, 531N, Univ. California, San Francisco, CA, 94143
Cancer Res; 41(11,part1):4426-4431 1981

An enzyme-activated irreversible inhibitor of ornithine decarboxylase, alpha-difluoromethylornithine (DFMO), was used alone and in combination with various single doses of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) to treat animals bearing the murine glioma 26 and rat 9L gliosarcoma intracerebral tumors. Used as a single agent, DFMO has little or no effect against these tumors. However, in both intracerebral tumor models, pretreatment with DFMO po before ip administration of BCNU potentiates the effect of BCNU without increasing toxicity. The effects of DFMO administered po after BCNU or before and after various doses of BCNU indicate that DFMO may also effectively slow the repopulation of these tumors after BCNU therapy. (Author abstract) (22 Refs)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

10. A PROTECTIVE EFFECT OF COENZYME Q10 ON THE ADRIAMYCIN-INDUCED CARDIOTOXICITY IN THE ISOLATED RAT HEART.

Ohhara H, Kanaide H, Nakamura M
Res. Inst. Angiocardiology, Kyushu Univ. Medical Sch., Kyushu, Japan
J Mol Cell Cardiol; 13(8):741-752 1981

Coenzyme Q10 (CoQ) was studied for possible protection of the heart from toxic effects of the antitumor agent adriamycin (A). Male Wistar rats were injected with 15 mg CoQ/kg body wt dissolved in a vehicle or with the vehicle alone daily for 1 wk. Hearts were then excised and perfused by Langendorff's technique with adriamycin for 60 min and then with normal buffer for 30 min. A produced dose-dependent reduction in contractile muscle tension and increase in resting tension. Coronary flow rate was reduced by A doses of 20 ug/ml for 60 min, 30 ug/ml for 60 min, and 50 ug/ml for 30 min by 58%, 7%, and 10% of pretreatment values, respectively. The effect was nearly negligible with 5 or 10 ug/ml. No change or recovery occurred during the A-free perfusion period. ATP, total adenine nucleotide, and creatine phosphate levels were reduced by A in hearts not pretreated with CoQ. AMP increased over normal values. CoQ pretreatment resulted in higher levels of ATP, total adenine nucleotide, and NAD than in vehicle-treated hearts, although these levels were not normal. Contractile muscle tension was greater and resting tension less in CoQ-treated hearts than in vehicle-treated hearts. Apparently CoQ protects the heart from the toxic effects of A by stabilizing various membranes, preventing loss of metabolic intermediates, and maintaining better ATP synthesis. (46 Refs)

11. ADRIAMYCIN EXPERIMENTAL CARDIOMYOPATHY IN SWISS MICE. DIFFERENT EFFECTS OF TWO CALCIUM ANTAGONISTIC DRUGS ON ADM - INDUCED CARDIOMYOPATHY.

Klugmann S, Bartoli Klugmann F, Decorti G, Gori D, Silvestri F, Camerini F
Dept. Cardiology, Ente Ospedaliero Regionale, Trieste, Italy
Pharmacol Res Commun; 13(8):769-776 1981

Effects of the calcium-antagonistic drugs verapamil (V) and nifedipine (N) were tested in order to clarify the pathogenic mechanism of adriamycin (ADM). Swiss mice were injected ip with ADM (2.78 mg/kg 3x/wk for 4 wk, total dose 33.4 mg/kg); some of the mice also received V (5, 10, or 20 mg/kg/day, po) or N (7.5 or 15 mg/kg/day po). Other mice received only V (20 mg/kg/day po), only N (15 mg/kg/day po), or no treatment. All mice receiving ADM showed dorsal and ventral alopecia, decreased ability to gain wt, and cardiomyopathy. Mean survival time was the same for ADM and ADM + V mice (43-53 days) and was significantly longer than that of ADM + N mice (31-32 days). Histological cardiac changes included vacuolization, nuclear pyknosis, myocytolysis, cytoplasmic homogeneity, and lack of evident cross striations in myocardial cells. Changes were more pronounced in cells from mice receiving ADM + N. Evidently calcium-antagonistic drugs do not prevent ADM-induced cardiomyopathy. V and N appear to have two different types of action ; N may have a synergistic effect with ADM. Results do not support the hypothesis that ADM-induced cardiomyopathy is the result of calcium overload. (29 Refs)

12. SOFT-TISSUE NECROSIS INDUCED BY EXTRAVASATED CANCER CHEMOTHERAPEUTIC AGENTS: A STUDY OF ACTIVE INTERVENTION.

Barr RD, Sertic J
McMaster Univ. Health Sciences Centre, Room 3N27D, 1200 Main St., Hamilton, Ontario L8S 4J9, Canada
Br J Cancer; 44(2):267-269 1981

The effect of various prophylactic agents on drug-induced soft tissue necrosis was studied in Hartley guinea pigs. Vincristine (VCR; 2.5 or 5.0 ug in 0.3 ml) was given id; adriamycin (ADR; various concentrations in 1.0 ml) was given sc. Secondary agents were given by the same route (id, in 1 ml; sc in 5 ml) either immediately or 24 hr after drug. The secondary agents included isotonic phosphate-buffered saline (PBS; pH 7.4), hydrocortisone (HYD), indomethacin (IND; 2.8 x 10(-7) M) and sodium bicarbonate (SB; 8.4%). None of the secondary agents were toxic after sc injection; IND and SB caused florid (necrotic) lesions when given alone id. PBS and HYD (25 mg) prevented local necrosis after 2.5 ug VCR when used at time of drug injection; when given after 24 hr, only HYD was effective. After 5.0 ug of VCR, immediate or delayed intervention was without effect. With ADR immediate or delayed intervention had no beneficial effect. (7 Refs)

13. REDUCTION IN RABBIT SERUM AND PULMONARY ANGIOTENSIN CONVERTING ENZYME ACTIVITY AFTER SUBACUTE BLEOMYCIN TREATMENT.

Lazo JS, Catravas JD, Gillis CN
Dept. Pharmacology, Section Developmental Therapeutics, Yale Univ. Sch. Medicine, P.O. Box 3333, 333 Cedar St., New Haven, CT, 06510
Biochem Pharmacol; 30(18):2577-2584 1981

We studied morphological and biochemical alterations in the lungs of rabbits treated sc with bleomycin (5 mg/kg) 3x weekly for 28 days. This treatment produced morphologically evident pulmonary damage characterized by the appearance of ciliated alveolar epithelial cells and endothelial blebs. No change in pulmonary collagen content was evident. Rabbits treated with bleomycin had significantly less pulmonary angiotensin converting enzyme activity than control animals, although no alterations in lung DNA, protein, glycosaminoglycans or hydroxyproline (an index of collagen) were observed. Serum angiotensin converting enzyme activity decreased with repeated bleomycin administration and was reduced by 42, 48 and 65% from control animals 2, 3 and 4 wk, respectively, after the initiation of drug treatment. these data provide biochemical evidence that subacute bleomycin administration damages the pulmonary endothelium in the absence of fibrosis and can reduce the serum activity of angiotensin converting enzyme in rabbits. (Author abstract) (40 Refs)

14. BIOCHEMICAL PROPERTIES OF GLOMERULAR BASEMENT MEMBRANE IN DAUNOMYCIN NEPHROSIS A ND NEPHROTOXIC SERUM NEPHRITIS.

Koide H, Soeda N, Ohno J
Div. Nephrology, Dept. Medicine, Juntendo Univ. Sch. Medicine, Tokyo, Japan
Renal Physiol; 4(2/3):102-107 1981

The chemical compositions of glomerular basement membranes (GBM) from normal rats and rats with nephrosis induced by daunomycin (DN), and nephrotoxic serum nephritis (NSN) were compared. Glomerulonephritis was induced in rats by injection of 1.2 mg daunomycin/100g body wt iv. Rats were killed after 3 wk when urinary protein excretion was greater than 400 mg/24 hr. NSN was induced by injection of rabbit antiserum against rat GBM (0.5 or 0.8 ml/100g body wt). Analysis of amino acid composition in DN rats showed a decrease in the amount of 4-hydroxyproline, glycine, methionine, and hydroxylysine, and an increase in the relative amounts of serine, glutamic acid, leucine, and arginine. The ratios of 3-hydroxyproline to 4-hydroxyproline (3HP/4HP) and 4-hydroxyproline to proline (4HP/P) were unchanged. GBM from NSN rats showed decreased 4-hydroxyproline, glycine, isoleucine, and half-cystine, and increased aspartic acid, threonine, serine, glutamic acid, alanine, leucine, tyrosine, hydroxylysine, and lysine. The 3HP/4HP ratio was the same as in controls, while the 4HP/P ratio was significantly reduced. Carbohydrate analysis showed an increase in glucosamine in DN GBM and decreased fucose content and increased sialic acid content in NSN GBM. NSN GBM also showed reduced glucosyl-galactosyl-hydroxylysine. Results suggest a decrease in the collagenous component and an increase in the non-collagenous component of GBM in DN and NSN. (8 Refs)

15. PRELIMINARY REPORT ON THE EFFECTS OF A FOUR DRUG CYTOTOXIC PROTOCOL ON WOUND HEALING IN THE RAT.

Hughes KB
E.N.T. Dept., British Military Hosp., Hong Kong BFPOI, China
Clin Oncol; 7(3):235-240 1981

Operative wound strengths in rats were examined after the administration of a drug protocol, containing bleomycin, 5-fluorouracil, methotrexate and vincristine. These drugs were given in combination on a kinetic basis with folinic acid rescue. Estimation of the bursting strengths of gastric and musculocutaneous wounds made on the fifth postoperative day showed significant reductions when compared to those in control animals. This has significant implications if the theoretical advantages of giving cytotoxic drugs in the immediate post-operative period in cancer surgery are to be implemented. (Author abstract) (16 Refs)

16. EVALUATION OF DOXORUBICIN TOXICITY ON NORMAL HEMOPOIETIC STEM CELLS.

Muzzulini C, D'Amore F, Sobrero A, Massa G, Bogliolo G, Ghio R, Pannacciulli I
I.S.M.I., Viale Benedetto xv, n. 6, 16100 Genova, Italia
Tumori; 67(4):293-300 1981

The effect of administration of Doxorubicin (Dx) on the bone marrow CFUs, CFUc and CFUe has been evaluated in mice following injection of scalar single doses of the drug or during its repeated (3x in 5 days) or prolonged (5 or 10 wk) administration. In the first experiment the dose survival curves were exponential and the sensitivity of the three types of hemopoietic progenitors assayed was almost similar. During repeated or prolonged administration of Doxorubicin the CFUs appeared to be less affected by the drug than the committed progenitors. (Author abstract) (22 Refs) (In ITA)

17. METHODS OF REDUCTION OF CISPLATIN NEPHROTOXICITY.

Walker EM
Dept. Lab. Medicine, Veterans Admin. Medical Center, Charleston, SC, 29425
Ann Clin Lab Sci; 11(5):397-410 1981

A review is presented of the pharmacology, toxicology, pharmacokinetics, nephrotoxicity, and reduction of toxicity of cisplatin, a platinum-containing compound that is effective against a number of animal tumor systems. The hypothesis explaining the nephrotoxicity of cisplatin states that: (1) it is a direct tubular toxicant, (2) it must be present in tubular urine at a min concentration of approx 1 mM for a given period of time (several hr) for irreversible damage to occur, and (3) its mechanism of toxicity probably is mediated via inhibition of (primarily) the Na, K-ATPase. Numerous treatments and substance have been examined for their ability to reduce cisplatin nephrotoxicity; these include hydration, diuresis, penicillamine, probenecid, superoxide dismutase, WR-2721, diethyldithiocarbamate, thiourea, thiosulfate, and other adjuncts, with favorable results in many cases. There are also platinum derivatives other than cisplatin that have equal or superior therapeutic potential and exhibit less nephrotoxicity. The possible role of prostaglandins in the reduction of cisplatin-induced nephrotoxicity is also discussed. (99 Refs)

18. CHRONIC INTRAVENOUS ADMINISTRATION OF LENTINAN TO THE RHESUS MONKEY.

Sortwell RJ, Dawe S, Allen DG, Street AE, Heywood R, Edmondson NA, Goginath C
Huntingdon Res. Centre, Huntingdon, Cambs, PE18 6ES, England
Toxicol Lett; 9(1):81-85 1981

The effects of lentinan, a polysaccharide with antitumor properties, were studied in the rhesus monkey. Four groups of monkeys, each consisting of three males and three females, received lentinan iv through the cephalic or saphenous vein. Dose level was 0.5, 2.0, 8.0, or 30.0 mg/kg/day. Injection vol was a constant 6 ml/kg. A fifth group received physiological saline injection. Treatment continued for 6 mo. One female receiving 30 mg/kg/day and suffering from severe ulcerative dermatitis was killed on day 20 for humane reasons. Doses of 30.0 or 8.0 mg/kg/day produced rashes, some ulcerative dermatitis, scleral hemorrhage, nose bleeding, fresh blood in feces, non-progressive anemia, and at the highest dose, slight suppression of body wt; hemorrhagic discoloration and congestion occurred in bladder mucosa and gast rointestinal tract, as well as in the heart, liver, kidneys, thymus, testes, and skeletal muscle. Foam cell reactions in the lungs, liver, kidney, spleen, lymph nodes, and bone marrow were seen at doses of 2.0 mg/kg/day or greater. The toxic effects of lentinan apparently reflected administration of large amounts of polysaccharide rather than specific toxicity of the compound. No effects were noted at a dose rate of 0.5 mg/kg/day. (3 Refs)

19. THE EFFECT OF LENTINAN ON PREGNANCY OF THE NEW ZEALAND WHITE RABBIT.

Cozens DD, Masters RE, Clark R
Huntingdon Res. Centre, Huntingdon, Cambs, PE18 6ES, England
Toxicol Lett; 9(1):65-70 1981

The effects of lentinan [(1 linked to 3)-beta-D-glucan], a polysaccharide with antitumor properties, were initially tested in sexually mature, nonpregnant New Zealand White rabbits injected iv with 0.5, 2.0, or 30.0 mg lentinan/kg/day for 21 days. At 30.0 mg/kg/day darkening and/or swelling of the nose, lips, eyelids, inner perimeter of the ear, sclera of the eye, and anogenital area, as well as loss of body wt and increased spleen wt were noted. At 0.5 mg/kg/day rabbits showed body wt recovery after day 4 and equivalence to controls by day 21. In a teratology study rabbits were injected iv with 0.1, 0.3, or 1.0 mg/kg/day from day 6 through day 18 of gestation. At 1.0 mg/kg/day some darkening of the eyelids, bruising of the ear, and swelling of the nose were noted in dams. Litter characteristics were not adversely affected: incidence of post-implantation loss, av litter size and wt, av fetal wt, and incidence of minor skeletal/visceral anomalies did not differ from control. Some increase in major fetal abnormalities occurred at 1.0 mg/kg/day, but this could not be attributed to lentinan treatment. (4 Refs)

20. THE EFFECT OF LENTINAN ON FERTILITY AND GENERAL REPRODUCTIVE PERFORMANCE OF THE RAT.

Cozens DD, Masters RE, Clark R, Offer JM
Huntingdon Res. Centre, Huntingdon, Cambs, Pe18 6ES, England
Toxicol Lett; 9(1):55-64 1981

The effect of lentinan [(1 linked to 3)-beta-D-glucan], a polysaccharide with antitumor properties, was studied in pathogen-free CrL COBS CD (SD) BR rats given 0.01, 0.10, or 1.0 mg lentinan/kg/day iv. Males were dosed for 9 wk and females for

2 wk before mating. Rats were (1) dosed until day 12 of pregnancy and killed on day 13, (2) dosed until day 19 and killed on day 20, or (3) allowed to deliver live pups and dosed until day 21 post partum. F1 rats did not receive lentinan except by exposure through dam's milk. Selected F1 rats were allowed to mature and were mated to produce F2 offspring. In F0 parent rats lentinan injections produced increased spleen wt, with evidence of macrophage infiltration. Males given a dose of 1.0 mg/kg/day showed reduced fertility and mean testicular wt, macroscopic evidence of epididymal and testicular changes, histological evidence of atrophic changes in the seminiferous tubules, chronic inflammation around testicular blood vessels, and formation of spermatocele granulomata and/or chronic inflammation of the epididymides. Effects were significantly less at a dose rate of 0.10 mg/kg/day. Some changes occurred at 0.01 mg/kg/day, but fertility was the same as in controls. Preweaning and post-weaning behavior and reproductive performance of F1 rats was not affected by lentinan treatment of the F0 generation. (13 Refs)

21. PULMONARY DAMAGE CAUSED BY CYTOSTATICS AND PARAQUAT.

Fischer G, Woltjen HH, Schauer A
Pathologisches Institut, Universitat Gottingen, Robert-Koch-Strasse 40, 3400 Gottingen, W. Germany
Roentgenblaetter; 34(9):331-337 1981

Pulmonary damage caused by certain cytostatics is reviewed. Early recognition of this partly toxic and partly allergic process is of great importance, because its progression to pulmonary fibrosis and respiratory insufficiency can be prevented only by discontinuing the treatment well in time. Pulmonary function tests permit early detection of functional disturbances in the affected lungs. Since the roentgenological findings are nonspecific even at advanced stages, final confirmation of the diagnosis is possible on lung biopsy only. Lungs damage by cytostatics show histologically characteristic but nonspecific patterns (interstitial edema, hyaline membranes, and atelectasis during the exudative phase, and lung fibrosis in the proliferative phase). Transition to the proliferate phase is characteristic of busulfan, while other cytostatics, especially methotrexate, usually cause self-limiting pulmonary damage. The frequency of pulmonary damage after bleomycin treatment is 3-5% at total doses of up to 300 mg, 10% for total doses exceeding 300 mg, and 20% for total doses above 500 mg. (43 Refs) (In GER)

22. GASTROINTESTINAL COMPLICATIONS OF CANCER CHEMOTHERAPY.

Semendiaeva ME, Petrovskii VS
Clinical Hosp. No. 6, Moscow, USSR
Sov Med; (7):70-76 1981

Literature data on the gastrointestinal toxicity of antineoplastic agents are reviewed. Antineoplastic agents were shown to induce toxic and allergic hepatitis. 5-Fluorouracil and mercaptopurine were found to change hemodynamics and inhibit the exocrine function of the pancreas. Drug-induced changes in the gastrointestinal mucosa were found to be associated with inhibition of serotonin release by enterochromaffin apparatus. The severity of gastrointestinal manifestations depends upon the mode and timing of drug administration. Selection of optimal doses and drug combinations, simultaneous administration of immunostimulants and protectors would reduce the toxicity of antineoplastic agents. (43 Refs) (In RUS)

23. DIFFERENCE IN EFFECTS OF VINBLASTINE AND VINCRISTINE ON THE DOG PLATELET AGGREGATION.

Takano S
Dept. Pharmacology, Fukushima Medical Coll., Fukushima 960, Japan
Tohoku J Exp Med; 135(1):79-85 1981

The effects of vinblastine (VB) and vincristine (VC) on aggregation and surface alteration of dog platelets were studied. Platelets were obtained from mongrel dogs of approx 10 kg. Platelets (6 x 10(5)/cubic mm plasma) were exposed to varying doses of VB or VC for different periods. At low concentrations (0.2-20 ug/ml), VB increased ADP-induced platelet aggregation but VC had no effect. VB augmentation of aggregation was greatest (46.3% compared with 26.5% for controls) at a VB concentration of 2 ug/ml. Aggregation was depressed to 14.7% by incubation with 100 ug VB/ml for 30 min. Controls showed 31.8% aggregation and VC-treated platelets 29.0%. VB at 100 ug/ml for 30 min produced 46.0% bumpy-form platelets, compared with 30.4% at 100 ug/ml VC. Platelets treated with VB for 15 min did not respond to ADP, while those exposed to VC for 30 min did aggregate. Apparently VC alters platelet surface formation without affecting aggregation capacity, indicating that membrane deformation is not always required for inhibition of aggregation. (8 Refs)

24. EYE TOXICITY OF CANCER CHEMOTHERAPY: A REVIEW OF THE LITERATURE.

Griffin JD, Garnick MB
(c/o Garnick), Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Cancer; 48(7):1539-1549 1981

Eye toxicity from cancer chemotherapy is uncommon, but important because of the debility caused by loss of vision. The literature describing eye toxicity is reviewed for commonly used antineoplastic agents. (Author abstract) (125 Refs)

PHARMACOKINETICS OF ANTITUMOR AGENTS

25. EXTRACTIVE ALKYLATION OF 6-MERCAPTOPURINE AND DETERMINATION IN PLASMA BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY.

Floberg S, Hartvig P, Lindstrom B, Lonnerholm G, Odlind B
Dept. Drugs, Natl. Board Health and Welfare, Box 607, S-751 25 Uppsala, Sweden
J Chromatogr; 225(1):73-81 1981

An analytical procedure was developed for the determination of 6-mercaptopurine in plasma. Owing to the polar character and low concentrations of the compound, extraction and derivatization was carried out directly from the plasma sample by extractive alkylation. Determination was made using gas chromatography-mass spectrometry with multiple-ion detection. Conditions with respect to the rate of formation and the stability of the derivative formed in the extractive alkylation step were evaluated. The selectivity of the method to azathioprine and to metabolites was thoroughly investigated. No 6-mercaptopurine was formed from azathioprine added to water or plasma and run through the method. The method enables the detection of 2 ng of 6-mercaptopurine in a 1.0-ml plasma sample. Quantitative determinations were done down to 10 ng/ml 6-mercaptopurine in plasma. (Author abstract) (20 Refs)

26. EXCRETION OF 1-HEXYLCARBAMOYL-5-FLUOROURACIL IN URINE OF MICE.

Iigo M, Nakamura A, Kuretani K, Hoshi A

Pharmacology Div., Natl. Cancer Center Res. Inst., 5-1-1 Tsukiji, Chuo-ku, Tokyo 104, Japan

J Pharmacobio Dyn; 4(7):490-496 1981

Metabolites and excretion of 1-hexylcarbamoyl-5-fluorouracil (HCFU) and 5-fluorouracil (FU) in urine and feces of female ddN mice after po administration were studied. The main metabolites of 14-C-labeled HCFU and FU found in the urine and identified by thin layer chromatography were FU, 1-(3-carboxypropylcarbamoyl)-5-fluorouracil, 5,6-dihydro-5-fluorouracil, and alpha-fluoro-beta-alanine. The excretion pattern of 14C-HCFU metabolites is described. Approx 90% of 14C-HCFU and 14C-FU was absorbed from the gastrointestinal tract, primarily from the stomach and duodenum, within 60 min of po administration. (8 Refs)

27. DETERMINATION OF CYTARABINE AND URACIL ARABINOSIDE IN HUMAN PLASMA AND CEREBROSPINAL FLUID BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY.

Breithaupt H, Schick J

Medizinische Klinik, Justus Liebig-Universitat, Klinikstrasse 36, 6300 Giessen, W. Germany

J Chromatogr; 225(1):99-106 1981

A high-performance liquid chromatographic method for the determination of the antineoplastic agent cytosine arabinoside and its main metabolite uracil arabinoside in human plasma and cerebrospinal fluid is described. Complete separation from endogenous constituents was achieved by isocratic reversed-phase chromatography using phosphate buffer (0.05 M, pH 7.0) as the eluent. The limit of detection was 50 ng/ml. Day to day coefficients of variation was below 10%. The applicability of this rapid, simple and specific method for pharmacokinetic studies and monitoring of therapy was demonstrated. (Author abstract) (37 Refs)

28. QUALITATIVE AND QUANTITATIVE ANALYSIS OF URACIL ANTICANCER DRUGS.

Hassib ST

Pharmaceutical Chemistry Dept., Faculty Pharmacy, Cairo Univ., Cairo, Egypt

Talanta; 28(9):685-687 1981

The selective identification and estimation of two anticancer drugs, 5-fluorouracil and uracil mustard, by two color reaction methods is described. The production of an orange-red precipitate following reaction of 5-fluorouracil with 2,4-dinitrophenylhydrazine (DNPH) in a borax medium in the presence of bromine is described. The DNPH derivative gives a characteristic violet color with aqueous KOH. When uracil mustard is heated with an aqueous soln of alpha-picoline to form a pyridinium salt which is condensed with sodium 1,2-naphthoquinone-4-sulfonate in the presence of alcoholic KOH a red color can be observed. (5 Refs)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

29. SYNTHESIS AND ANTINEOPLASTIC ACTIVITY OF MITOSENE ANALOGUES OF THE MITOMYCINS.

Hodges JC, Remers WA, Bradner WT

Dept. Pharmaceutical Sciences, Coll. Pharmacy, Univ. Arizona, Tucson, AZ, 85721

J Med Chem; 24(10):1184-1191 1981

A series of 1-substituted mitosene analogues of the mitomycin antitumor antibiotics was prepared by total synthesis and screened for activity against P388 leukemia in mice. In general, analogues with moderately good leaving groups (mostly esters) at the 1 position were active, whereas analogues without such substituents were inactive or barely active. These results lend support to the idea that mitosenes with leaving groups at position 1 are capable of bifunctional alkylation of DNA in a manner similar to that of mitomycin C. The most active mitosenes were equal in potency (minimum effective dose) to a corresponding aziridinomitosene, but they were less effective in prolonging life span. (Author abstract) (16 Refs)

30. SEARCH FOR ANTITUMOR COMPOUNDS. XIII. BIOLOGICAL STUDIES. ANTITUMOR PROPERTIES OF 20 QUINOLINES, CARBAZOLES, ACRIDINE NITRO DERIVATIVES.

Hrabowska M, Ledochowski A, Wysocka-Skrzela B, Onoszko K, Paradziej-Lukowicz J

Lab. Chemistry and Biochemisty of Antitumor Compounds, Inst. Organic and Food Chemistry and Technology, Polytechnical Univ., 80-952 Gdansk, Poland

Arch Immunol Ther Exp (Warsz); 29(2):205-216 1981

The antitumor activity of 19 ledakrin (nitrocridine) analogs was tested in mice bearing sarcoma 180. All 1-nitro-9-aminoacridine derivatives (C-258, C-828, C-874, C-899) caused a significant dose-related inhibition of tumor growth. Two acridone derivatives (C-753, C-755) also inhibited tumor growth, but in doses 1-100x higher than the effective ledakrin dose. The remaining compounds, including nitrocarbazoles, nitro-4-aminoquinoline derivatives, and other acridone derivatives were inactive. Histological studies showed that the 1-nitro-9-aminoacridine derivatives influenced tumor mitotic activity, behavior of polynuclear WBC and macrophages in the invasion zone surrounding the sarcoma, and the composition of PAS-positive ground substance in this zone. (21 Refs)

31. ANALYSIS OF MEDICINAL COMPONENTS IN AN HERB USED TO CONTROL CANCER. PART 2. ON THE CONSTITUENTS OF HEDYOTIS CORYMBOSA LAM..

Takagi S, Yamaki M, Masuda K, Nishihama Y, Sakina K

Mukogawa Women's Univ. Faculty of Pharmaceutical Sciences, Edagawa-cho, Nishinomiya, Hyogo Prefecture, Japan

Yakugaku Zasshi; 101(7):657-659 1981

Six iridoids, asperuloside, scandoside methyl ester, asperulosidic acid, geniposidic acid, scandoside, and deacetylasperulosidic acid and six glucosides were isolated from Hedyotis corymbosa LAM, an herb used to control some forms of cancer in China. Three new types of iridoids were extracted from H corymbosa LAM, and their pharmacological properties are under investigation. (8 Refs) (In JPN)

32. SYNTHESIS, TOXICITY, AND ANTITUMOR ACTIVITY OF CARMINOMYCIN AZINE (CARMINAZINE).

Povarov LS, Gol'dberg LE, Bazhanov VS, Shepelevtseva NG, Vertogradova TP, Averbukh LA
All-Union Res. Inst. Screening for New Antibiotics, Moscow, USSR
Antibiotiki; 26(8):620-623 1981

Toxicity and antitumor activity of newly synthesized carminomycin (CM) derivative carminazine (CZ: carminomycin azine) were studied in random-bred albino mice. CZ was 2x less toxic than CM after iv administration and 7x less toxic after po administration. CZ was 1.8x less effective against lymphosarcoma LIO-1 than CM. (5 Refs) (In RUS)

33. INTERACTION OF 1-(5-PHOSPHO-BETA-D-ARABINOFURANOSYL)-5-SUBSTITUTED URACILS WITH THYMIDYLATE SYNTHETASE: MECHANISM-BASED INHIBITION BY 1-(5-PHOSPHO-BETA-ARABINOSYL)-5-FLUOROURACIL.

Nakayama C, Wataya Y, Santi DV, Saneyoshi M, Ueda T
Faculty Pharmaceutical Sciences, Hokkaido Univ., Sapporo 060, Japan
J Med Chem; 24(10):1161-1165 1981

A number of 1-(5-phospho-beta-D-arabinosyl)-5-substituted-uracils (ara-UMP's) have been examined as inhibitors of dTMP synthetase. As reversible inhibitors, all were substantially less potent than their 2'-deoxyribosyl counterparts. In the presence of 5,10-methylenetetrahydrofolate (CH2-H4folate), ara-FUMP caused a first-order, time-dependent inactivation of the enzyme. At 0 C, kinetic studies indicated a reversible Kd of 3.6 uM for the ara-FUMP-CH2-H4folate complex, and kappa = 0.22 min-1 for the subsequent inactivation. Spectral studies of the complex and its behavior toward protein denaturants demonstrate that its structure and stoichiometry are directly analogous to those which have previously been described for FdUMP. The significance of this finding with regard to prodrugs of ara-FU and the potential of ara-FU as a chemotherapeutic agent are discussed. (Author abstract) (33 Refs)

34. IN VITRO SCREENING OF POTENTIAL ANTICANCER CHEMICALS: EFFECT OF PURINE PYRIMIDINE ANALOGUES ON SEED GERMINATION.

Dwivedi CM, Junjappa H, Murti CR
(c/o Murti), Industrial Toxicology Res. Centre, Post Box No. 80, Mahatma Gandhi Marg, Lucknow-226 001, India
Toxicology; 21(3):251-260 1981

The effect of various purine and pyrimidine analogues on the germination of Cicer arietinum and Escherichia coli dihydrofolate reductase (DHFR) is reported. Initial experiments with adenine, guanine, cytosine, uracil, and thymidine (1 milliM) did not show any effect on germination at 144 hr; their analogues were quite active. Mercaptopurine stimulated germination, xanthine had no effects, and 8-azaadenine, 8-azaguanine, 2,6-diaminopurine, and 2-hydroxypurine were potent inhibitors (83-93% inhibition). 5-Aminouracil, 6-methyluracil, and methylxanthines (eg caffeine, theophylline, theobromine, and uric acid) exhibited lesser (27-44%) inhibitory effects. 5-Fluorouracil blocked germination at 144 hr to about 90%. The effect of these purine and pyrimidine analogues on RNA synthesis, judged by (2-14C)uracil incorporation, is also presented. Cyclic AMP, adenosine, indole-3-acetic acid, and folic acid partially reversed purine and pyrimidine analogue inhibition of germination. Several newly synthesized pyrimidine analogues inhibited germination and RNA synthesis. A close analogy between interference with germination and inhibition of DHFR was observed. (32 Refs)

35. CHEMICAL AND BIOLOGICAL STUDIES ON 5,6-EPOXYRETINOL, RETINOL, AND THEIR PHOSPHORYL ESTERS.

Bhat PV, Roller PP, De Luca LM
(c/o De Luca), NCI, NIH, Building 37, Room 2B26, Bethesda, MD, 20205
J Lipid Res; 22(7):1069-1078 1981

Studies are reported on chemical synthesis, UV absorption spectral characteristics, and mass spectral fragmentation of 5,6-epoxyretinol and 5,6-epoxyretinylphosphate. These compounds were separated from each other and from other retinoids by a reverse phase high pressure liquid chromatographic system. A comparative study on the lability to acid of 5,6-epoxyretinylphosphate and retinylphosphate was conducted. The retroretinoid anhydroretinol is formed chemically from retinylphosphate by acid hydrolysis and biologically from retinol in cultured, spontaneously-transformed mouse fibroblasts, 3T12 cells. Similarly, acid hydrolysis of 5,6-epoxyretinylphosphate (absorption maxima 324, 310, 296 nm) in methanol yielded a low polarity retinoid with absorption maxima at 364, 346, and 330 nm, similar to the absorption spectra of retrovitamin A1 and retrovitamin A2. Mass spectral analysis was found to be in agreement with a retrostructure and permitted identification of the compound as a methoxyretrovitamin A1 methyl ether. A similar retroretinoid was formed biologically from 5,6-epoxyretinol in spontaneously-transformed mouse 3T12 cells. Thus, it appeared that these cells have the ability to convert the primary alcohols into retroretinoids, which are also formed by acid treatment of the phosphate esters. The adhesive properties of 3T12 cells were highly enhanced by culturing in the presence of 10(-6) to 10(-5) M 5,6-epoxyretinol or -retinoic acid, in analogy with the response of these cells to the parent retinoids. Moreover, in another test of biological activity, 5,6-epoxyretinylphosphate functioned as a highly active acceptor of [14C]D-mannose from GDP-[14C]mannose in a reaction catalyzed by rat liver membranes. Thus, 5,6-epoxyretinoids appear to be as active as the parent retinoids in these in vitro tests of biological activity, even though they do not replace vitamin A in its growth function in vivo. (Author abstract) (20 Refs)

36. POTENTIAL ANTIESTROGENS. SYNTHESIS AND EVALUATION OF MAMMARY TUMOR INHIBITING ACTIVITY OF 1,2-DIALKYL-1,2-BIS(3'-HYDROXYPHENYL)ETHANES.

Hartmann RW, Buchborn H, Kranzfelder G, Schonenberger H, Bogden A
Inst. Pharmacy, Univ. Regensburg, Universitatsstrasse 31, 8400 Regensburg, W. Germany
J Med Chem; 24(10):1192-1197 1981

The synthesis of the meso-1,2-dialkyl-1,2-bis(3'-hydroxyphenyl)ethanes [alkyl substituent: CH3 (19), C2H5 (20), C3H7 (22), C4H9 (23), i-C4H9 (24), and C5H11 (25)] and of d,l-3,4-bis(3'-hydroxyphenyl)hexane (21) are described. In vitro these compounds inhibited the [3H]estradiol receptor interaction competitively, exhibiting Ka values between 0.20 x 10(9) (20) and 0.11 x 10(6) M-1 (24). In vivo the meso compounds reduced the estrone-stimulated mouse uterine growth; the most effective compounds were 20, 22, and 23 (53, 50, and 45% inhibition, respectively). Compounds 20 and 22-24 showed weak estrogenic activity in the mouse uterine wt test and in the vagina cornification test. Compounds 19 (NSC-297169), 20 (NSC-287170), and 22 (NSC-297171) exhibited a dose-dependent growth inhibition on the MCF-7 human breast tumor cell line (10(-6) to 10(-9) M). These compounds also showed a marked dose-dependent inhibition on the DMBA-induced, hormone-dependent mammary carcinoma of the Sprague-Dawley rat corresponding to their association constants. (Author abstract) (19 Refs)

37. CYTOTOXIC EFFECT OF ONION EXTRACT ON MOUSE FIBROSARCOMA 180 A CELLS.

Nerkar DP, Chander R, Bandekar JR, Tewari GM, Bandyopadhyay C
Biochemistry and Food Technology Div., Bhabha Atomic Res. Centre, Bombay 400 085, India
Indian J Exp Biol; 19(7):598-600 1981

The antitumor activities of onion extract (OE) and lacrimatory factor (LF) were investigated in mouse fibrosarcoma 180 cells (MFS-1). Cytotoxicity of OE was related to its concentration and time of incubation with ascites cells; cytotoxic effect as a function of concentration was nonlinear. Swiss male mice injected with cells which were treated with 150-200 ug OE for 3 hr did not develop tumors, while those treated with 50-100 ug OE did form ascites tumor. OE was cytotoxic to spleen cells and macrophages at doses of 200 ug/ml or more, while OE at doses as high as 450 mg/ml were nontoxic in vivo. When mice were transplanted with MFS-180 cells followed by three or four consecutive injections of 45 mg/kg/mouse starting at 0, 1, 2 or 4 days after transplantation, survival time of mice given OE on day 0 was extended over that of controls with only marginal effect in the other groups. LF appeared to be more cytotoxic than OE to MFS-180 cells. However, no significant prolongation of survival time of mice given LF was noted over controls. (12 Refs)

STUDIES OF ANTIMETASTATIC AGENTS

38. INHIBITION OF THE PLATELET-AGGREGATING ACTIVITY OF TWO HUMAN ADENOCARCINOMAS OF THE COLON AND AN ANAPLASTIC MURINE TUMOR WITH A SPECIFIC THROMBIN INHIBITOR, DANSYLARGININE N-(3-ETHYL-1,5-PENTANEDIYL)AMIDE.

Pearlstein E, Ambrogio C, Gasic G, Karpatkin S
(c/o Karpatkin) Dept. Medicine, New York Univ. Medical Sch., New York, NY, 10016
Cancer Res; 41(11,part1):4535-4539 1981

Platelets are required for certain experimental metastases. Several lines of animal tumor cells aggregate platelets in vitro and in vivo. Previous studies with one of these lines, an SV40-transformed 3T3 mouse fibroblast (SV3T3) have revealed that the platelet-aggregating material is an extractable membrane-associated sialolipoprotein which requires divalent cation, complement, and a heat-stable plasma component for activity. Little information is available on the interaction of human tumors with platelets. We now report on the ability of two human adenocarcinomas of the colon (LoVo and HCT-8) and an anaplastic mouse tumor (Hut-20) to aggregate platelets by a different mechanism, the generation of thrombin. These spontaneous cell lines aggregate human or rabbit platelet-rich plasma after a 1-to 2-min lag period. This is often followed by a visible clot. Unlike SV3T3 cells, aggregation by LoVo, HCT-8, and Hut-20 cells is not inhibited by neuraminidase, trypsin, or cobra venom factor. These three cell lines markedly shorten the recalcification time of citrated plasma, whereas SV3T3 cells do not. Phospholipase A2 treatment inhibits the shortening of the recalcification time for the three tumors; this parallels its inhibitory effect on platelet aggregation. LoVo, HCT-8, and Hut-20 cells generate thrombin via the 'tissue factor' coagulation pathway (using coagulation factor-deficient substrates). Dansylarginine-N-(3-ethyl-1,5-pentanediyl)amide, a highly specific, potent antithrombin antagonist, inhibits LoVo-, HCT-8-, and Hut-20-induced platelet aggregation at 4 to 15 uM, whereas its effect on SV3T3 cells is negligible. If platelets are required for certain human tumor metastases, dansylarginine-N-(3-ethyl-1,5-pentanediyl)amide, or other antithrombin agents, may prove to be valuable therapeutic agents. (Author abstract) (37 Refs)

39. EFFECTS OF 5(2-CHLOROBENZYL)-4,5,6,7-TETRAHYDROTHIENO[3,2 C]PYRIDINE HYDROCHLORIDE (TICLOPIDINE), A PLATELET AGGREGATION INHIBITOR, ON BLOOD-BORNE METASTASIS.

Kohga S, Kinjo M, Tanaka H, Ogawa M, Ishihara M, Tanaka N
(c/o Tanaka) Res. Inst., Daiichi Pharmaceutical Co., Edogawa-ku, Tokyo 132, Japan
Cancer Res; 41(11,part1):4710-4714 1981

A new platelet aggregation inhibitor compound, 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2 C]pyridine hydrochloride (ticlopidine), was examined for its inhibitory effects on blood-borne metastasis using three different rodent tumors (B16 melanoma, Lewis lung carcinoma, and rat ascites hepatoma, AH130). Ticlopidine was administered po to the rodents. It inhibited the aggregation of platelets induced by ADP, thrombin, crude extract of AH130, and viable AH130 and B16 melanoma cells and also resulted in a significant decrease of pulmonary metastasis induced by iv injection of B16 melanoma and AH130. Spontaneous pulmonary metastasis of Lewis lung carcinoma was also inhibited by po administration of ticlopidine. This new compound may be a useful agent for inhibiting platelet aggregation caused by various agents and for suppressing hematogenous pulmonary metastasis. (Author abstract) (23 Refs)

INTERFERON AND OTHER ANTIVIRALS

40. EFFECTS OF HUMAN LYMPHOBLASTOID INTERFERON ON CULTURED BREAST CANCER CELLS.

Shibata H, Taylor-Papadimitriou J
(c/o Taylor-Papadimitriou), Imperial Cancer Res. Fund, Post Office Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
Int J Cancer; 28(4):447-453 1981

The effect of human interferon on growth and fibronectin production in a range of cultured breast cancer cell lines has been investigated. The cell lines differ in their sensitivity to interferon's growth-inhibitory effect as determined from growth curves, but the degree of sensitivity varies according to the method of assay. When growth was measured in cultures seeded with fairly large numbers of cells, five out of seven lines examined showed a reduction of 50% or more in the number of attached cells after treatment for 8 days with 1,000 units/ml of interferon. Growth of the two cell lines least affected by interferon treatment in dense culture could, however, be markedly inhibited under conditions of clonal growth in agar or when sparsely seeded on plastic and this was due to inhibition of initiation of growth. In some breast epithelial lines, where the number of attached cells was regulated in part by cell shedding, it was found that interferon not only inhibited cell proliferation, but also increased cell shedding. To determine if interferon increased cell shedding by affecting fibronectin production, the total and cell associated fibronectin was estimated in control and interferon-treated cultures. Four of 10 cell lines examined produced detectable amounts of fibronectin, and in only 1 of these lines, Hs578T derived from a carcinosarcoma, was the production and retention of fibronectin inhibited by interferon treatment. In those breast carcinoma lines which produced detectable amounts of fibronectin, the level of production and retention of the protein, expressed as a proportion of the total protein, did not change after interferon treatment, but showed an increase if expressed on a per cell basis. This is explained by the fact that the interferon-treated cells showed an increase in cell vol. (Author abstract) (36 Refs)

41. INTERFERON PRODUCTION AFTER DIFFERENT METHODS OF ADMINISTRATION OF MODIFIED POLY(I)-POLY(C).

Andzhaparidze OG, Bektemirov TA, Burgasova MP, Ogleznev KIa
Res. Inst. Viral Preparations, Moscow, USSR
Vopr Virusol; (4):407-410 1981

Analysis of interferon (IF) titers after iv, im, subconjunctival, and endolumbar administration of modified poly(I)-poly(C) to Macaca mulatta showed similar patterns of IF production. Max titers were recorded at the site of inoculation. (7 Refs) (In RUS)

42. ANTIVIRAL AND ANTICELLULAR ACTIVITY OF HUMAN LEUKOCYTE AND FIBROBLAST INTERFERONS IN HOMOLOGOUS AND HETEROLOGOUS CELLS.

Orlova TG, Zhdanova LV, Timofeev IV, Indikova IN, Mentkevich LM, Malinovskaia VV, Balandin IG, Kuznetsov VP
N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Vopr Virusol; (4):404-407 1981

The antiviral and antiproliferative activities of human WBC and fibroblast interferons (IFs) were tested in human and cattle embryo tracheal cells. The activity of the WBC IF in the homologous cells was similar to that in the heterologous cells. The fibroblast IF was active in the homologous cells but failed to produce antiviral or antiproliferative effects in the heterologous cells. (18 Refs) (In RUS)

43. INTERFERON-INDUCING AND ANTIVIRAL ACTIVITY OF LEVAMISOLE.

Ershov FI, Grigorian SS, Kremerman IB, Nikolaeva OV
D. I. Ivanovskii Inst. Virology, Moscow, USSR
Antibiotiki; 26(8):617-620 1981

The interferon (IF)-inducing activity of levamisole (LM) was studied in random-bred-albino mice. The peak of IF (320-640 IU/ml) in the blood plasma was recorded 4-6 hr after LM administration (100 mg/kg, po). LM provided a 35-40% protection against tick-borne encephalitis. LM was ineffective against influenza virus. (13 Refs) (In RUS)

OTHER RELATED STUDIES

44. EVALUATION OF EXPERIMENTAL PARAMETERS IN AN S9/HUMAN LEUKOCYTE SCE TEST WITH CYCLOPHOSPHAMIDE.

Madle S
Institut fur Genetik, Freie Universitat Berlin, Arnimallee 5-7, D 1000 Berlin 33, E. Germany
Mutat Res; 85(5):347-356 1981

The effect of various cyclophosphamide (CP) concentrations on sister chromatid exchange (SCE) frequency and cell proliferation, and the influence of experimental parameters (S9 concentration, concentration of cofactors, and exposure time) on CP-induced effects were examined in a human WBC test. The S9 fraction was prepared from livers of Aroclor-induced male rats. S9 mix alone did not influence SCE frequency or cell proliferation. CP, 1.7 x 10(-6) to 5.0 x 10(-5) M, produced increasing delay in cell proliferation. CP-induced SCE frequencies were strongly dependent on actual S9 concentration; cell proliferation was delayed with increasing S9 concentration. Studies with different concentrations of the cofactors (NADP and glucose-6-phosphatase in a ratio of 1:2) indicated an influence on the activity of S9 mix which was not as important as S9 concentration: SCE frequency increased, but cell proliferation was slightly inhibited with prolonged exposure times. CP at 1.7 x 10(-5) M was toxic in exposures greater than 2 hr. The importance of varying experimental parameters to avoid false-negative results in microsome tes ts is discussed. (28 Refs)

45. ENHANCEMENT OF MACROPHAGE-INDUCED CYTOTOXICITY BY PHORBOL ESTER TUMOR PROMOTERS.

Laskin DL, Laskin JD, Kessler FK, Weinstein IB, Carchman RA
(c/o Carchman) Dept. Pharmacology, Medical Coll. Virginia, Richmond, VA, 23298
Cancer Res; 41(11,part1):4523-4528 1981

The potent tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), markedly enhanced the ability of mouse peritoneal macrophages to inhibit the growth of L5178Y tumor cells as measured by growth in agar. Three populations of macrophages, resident, divinylether maleic anhydride copolymer, and thioglycollate-recruited, were used. In general TPA reduced both the cocultivation time and the number of macrophages required to induce cytotoxicity in all three macrophage types. With divinylether maleic anhydride copolymer macrophages, TPA enhanced cytotoxicity in a dose-dependent manner in the concentration range of 1.7 to 170 nM at macrophage:tumor cell ratios of 10:1 and 1:1. For reasons that were not apparent, inhibition of cytotoxicity was found at higher cell ratios. With both thioglycollate-elicited and resident macrophages, TPA (170 nM) enhanced cytotoxicity at all ratios tested. Even 1:1 ratios of macrophages:tumor cells, which were not cytotoxic alone, inhibited cell viability by 50% to 60% in the presence of TPA. A correlation was found between the biological activity of related macrocyclic diterpenes and their ability to enhance macrophage-mediated cytotoxicity. Thus, mezerein and phorbol didecanoate enhanced macrophage cytotoxicity, while the biologically inactive analogs, phorbol, 4-O-methyl-12-O-tetradecanoylphorbol-13-acetate, and 4-alpha-phorbol-12,13-didecanoate were without effect in this assay. Cytotoxicity towards untransformed BALB/c/3T3 cells was also demonstrated using a liquid cloning assay. These target cells were much less sensitive to growth inhibition by the macrophages than were the L5178Y cells. A 50% decrease in survival occurred only after 48 hr incubation and required macrophage:target cell ratios of 100:1. The addition of 170 nM TPA led to a dramatic enhancement of cytotoxicity in these cells at macrophage:target cell ratios of 10:1 and 1:1. The results observed with the phorbol esters in the present studies are compatible with other evidence that these compounds can modulate a variety of macrophage functions. (Author abstract) (50 Refs)

46. MEMBRANE AFFINITY AND METABOLISM OF N4-PALMITOYL-1-BETA-D-ARABINOFURANOSYLCYTOSINE INTO CULTURED KB CELLS.

Tsuruo T, Iida H, Hori K, Tsukagoshi S, Sakurai Y
Cancer Chemotherapy Center, Japanese Foundation for Cancer Res., Toshima-ku, Tokyo 170, Japan
Cancer Res; 41(11,part1):4484-4488 1981

N4-Palmitoyl-1-beta-D-arabinofuranosylcytosine (N4-palmitoyl-ara-C), a lipophilic derivative of 1-beta-D-arabinofuranosylcytosine, possessed an affinity for KB cell plasma membrane. Approx 15 to 25% of the drug incorporated into KB cells was retained in plasma membrane when the cells were treated with the drug for 1 to 32 hr at 10 uM, the concentration required for 50% inhibition of cell growth. Less than 5.3% of the drug was found in the plasma membrane when the cells were treated with 1-beta-D-arabinofuranosylcytosine. N4-Palmitoyl-ara-C in the membrane fraction cosedimented with plasma membrane in a sucrose density gradient at 4 C, indicating a close association between the drug and the membrane. The affinity of N4-palmitoyl-ara-C for plasma membrane probably contributes to the efficient uptake rate and the strong cytotoxic effect of N4-palmitoyl-ara-C reported previously. The metabolites of N4-palmitoyl-ara-C in KB cells, treated with the drug for 32 hr at the concentration required for 50% inhibition of cell growth (10 uM), were analyzed by diethylaminoethyl Sepharose CL-6B column chromatography and thin-layer and paper chromatography. This analysis showed that over 98% of the drug present in the KB cell was N4-palmitoyl-ara-C. The active metabolites, 1-beta-D-arabinofuranosylcytosine, 1-beta-D-arabinofuranosylcytosine 5'-monophosphate, N4-palmitoyl-1-beta-D-arabinofuranosylcytosine 5'-monophosphate, and 1-beta-D-arabinofuranosylcytosine 5'-triphosphate, were found in amounts of 0.41, 0.37, 0.17, and 0.05%, respectively, of the total drug found in the cells. Also found were the inactive metabolites 1-beta-D-arabinofuranosyluracil and 1-beta-D-arabinofuranosylcytosine diphosphate choline in amounts of 0.61 and 0.29%, respectively. (Author abstract) (27 Refs)

47. IDENTIFICATION OF THE MECHANISM OF ACTIVATION OF 9-BETA-D-ARABINOFURANOSYLADENINE IN HUMAN LYMPHOID CELLS USING MUTANTS DEFICIENT IN NUCLEOSIDE KINASES.

Verhoef V, Sarup J, Fridland A
(c/o Fridland) St. Jude Children's Res. Hosp., 332 Lauderdale, P.O. Box 318, Memphis, TN, 38101
Cancer Res; 41(11,part1):4478-4483 1981

The biochemical basis of cellular resistance to 9-beta-D-arabinofuranosyladenine (ara-A) and its natural purine derivative, deoxyadenosine, was investigated with two mutants of cultured human T-lymphoblastoid CCRF-CEM cells. One mutant that lacked deoxycytidine kinase activity, designated CEM/ara-C, retained about 10% of wild-type deoxyadenosine kinase and deoxyguanosine kinase activity each but maintained normal adenosine kinase or thymidine kinase activity. This suggested that in these human T-lymphoblastoid cells, as in other previously studied mammalian cells, deoxycytidine and purine deoxyribonucleosides are phosphorylated by the same enzyme. Despite this extensive reduction of purine nucleoside kinase activities, the cytotoxicity of ara-A or deoxyadenosine was not appreciably affected, decreasing by only 2.5-and 6-fold, respectively. A second mutant, isolated by selecting CEM/ara-C mutants that were resistant to ara-A, showed a 100-fold increase in resistance to ara-A cytotoxicity. This ara-A-resistant subline was deficient in the activities of two enzymes, deoxycytidine kinase and adenosine kinase, and showed a high degree of resistance to deoxyadenosine, adenosine, and pyrazofurin but not to pyrimidine analogs, such as 5-fluorodeoxyuridine or 5-fluorouridine. Further studies of ara-A and deoxyadenosine phosphorylation in wild-type and resistant cell lines disclosed that, although deoxycytidine kinase is the principal enzyme for their phosphorylation in vitro, their intracellular conversion to cytotoxic nucleotides depends on the joint action of deoxycytidine kinase and adenosine kinase rather than purine-specific deoxynucleoside kinase, as previously thought. (Author abstract) (27 Refs)

48. INTERACTIONS BETWEEN TUMOR SUBPOPULATIONS AFFECTING THEIR SENSITIVITY TO THE ANTINEOPLASTIC AGENTS CYCLOPHOSPHAMIDE AND METHOTREXATE.

Miller BE, Miller FR, Heppner GH
Dept. Immunology, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 41(11,part1):4378-4381 1981

The hypothesis that individual tumor subpopulations which differ in sensitivity to chemotherapeutic agents can influence each other's drug sensitivity was investigated using a set of mouse mammary tumor subpopulations derived from the same tumor. In one set of experiments, syngeneic mice were given injections of cyclophosphamide (CY)-sensitive line 168 cells and relatively insensitive line 410 cells on opposite flanks. Other mice received bilateral injections of only 168 or only 410 cells. CY administration was begun 2 days later and continued once a wk for 4 wk. The sensitivity of line 168 tumors was not affected by line 410 tumors, but the sensitivity of line 410 tumors was increased by the presence of line 168 tumors. The ability of line 168 tumors to increase the CY-sensitivity of line 410 tumors was not altered by irradiating (400 rads) the hosts 2 days before tumor cell injection. Mice bearing line 168 tumors only or both line 168 and line 410 tumors were more sensitive to the acute toxic effects of single, high doses of CY than were the line 410 tumor-bearing mice, suggesting that effects on CY activation are responsible for the drug sensitivity interaction. In a second set of experiments, cells of subpopulations which differed in sensitivity to methotrexate (MTX) were cocultured in vitro in the presence or absence of MTX. In the presence of MTX-sensitive line 410.4 cells, the sensitivity of cells of lines 67 and 168 was increased. The sensitivity of cells of another relatively insensitive population, T68H clone 8, was not affected. Thus, the sensitivity of some mammary tumor subpopulations to both CY and MTX can be influenced by the presence of other subpopulations that differ, when tested alone, in sensitivity to these agents. (Author abstract) (21 Refs)

49. STUDIES ON THE RESISTANCE OF A MURINE LEUKEMIA L1210 CELL LINE TO CIS-DIAMMINEDICHLOROPLATINUM (II).

Eastman A, Bresnick E

Dept. Biochemistry, Univ. Vermont Coll. Medicine, Given Bldg., Burlington, VT, 05405

Biochem Pharmacol; 30(19):2721-2723 1981

The possible cross-resistance of both cis-diamminedichloroplatinum (II) (cis-DDP)-sensitive (L1210/0) and -resistant (L1210/DDP) cells from the murine leukemia L1210 cell line to a variety of DNA damaging agents was analyzed. In the L1210/DDP cell line, a 30-fold resistance to cis-DDP and cis-dichloroethylenediamineplatinum (II) was observed, whereas only a 2-fold change in sensitivity to trans-diamminedichloroplatinum (II) was apparent. Resistance, therefore, seemed to be specific for the active chemotherapeutic drug rather than for the ineffective isomer. This resistance was also phenotypically stable as L1210/DDP cells have been grown for 80 doublings in the absence of cis-DDP without change in sensitivity. L1210/DDP cells showed the same sensitivity to melphalan as did sensitive L1210 cells. Aziridinyl benzoquinone affected both the sensitive and resistant strains similarly. Neocarzinostatin, a protein antibiotic that causes breakage of DNA in cultured cells and degradation of extracted DNA, was equally toxic to the two cell lines. Two direct-acting methylating agents, methyl methanesulfonate and N-methyl-N'-nitro-N-nitrosoguanidine, were also tested, but neither exhibited cross-resistance. UV irradiation was also equitoxic to the two cell lines. No process sensitive to caffeine was observed in either sensitive or resistant L1210 cells. (14 Refs)

50. (NA+ + K+)-STIMULATED ATPASE OF HUMAN KIDNEY, NORMAL AND ADENOCARCINOMA. PHOSPHORYLATION AND INHIBITION BY ANTITUMOR PROTEINS.

Zaheer A, Singh D, Montgomery R

Dept. Biochemistry, Univ. Iowa, Iowa City, IA, 52242

Biochem Biophys Res Commun; 102(1):86-92 1981

To evaluate the effect of antitumor proteins on metabolism of cultured tumor cells, (Na+ + K+)-stimulated ATPase isolated from normal human kidney and from renal clear cell adenocarcinoma was treated with macromomycin (MM), auromomycin (AM), largomycin (LM), and NSC 327459. MM, LM, and NSC 327459 (all 50 ug/ml) caused 73.4-93.4% inhibition of enzyme purified from adenocarcinoma. LM and NSC 327459 produced 16.5-23.2% inhibition of the enzyme from normal kidney, but MM and AM did not affect normal kidney ATPase. AM was also ineffective against the enzyme from kidney adenocarcinoma. Cyclic AMP (5 uM) caused a 6x stimulation of the rate of phosphorylation of normal enzyme, compared with a 3x increase of phosphorylation rate for the tumor enzyme. Phosphorylation reduced the enzyme activities: the normal ATPase exhibited 28.8% of original activity and the tumor enzyme showed only 19.1%. The normal enzyme was now sensitive to M M inhibition (approx 40% at 10 ug/m). (16 Refs)

51. INHIBITION BY LYMPH NODE CELLS AND PROMOTION BY FETAL HEPATOCYTES OF MURINE TUMOURS WITHOUT OR WITH CHEMOTHERAPY.

Floersheim GL, Torhorst J
Zentrum fur Lehre und Forschung, Kantonsspital, Hebelstr. 20, CH-4031 Basel, Switzerland
Oncology; 38(6):321-328 1981

The growth of a syngeneic Moloney lymphoma in CBA mice was inhibited by the injection of lymph node cells from normal CBA donors. This cytotherapeutic effect was also seen after chemotherapy with cyclophosphamide (CY) or dimethylmyleran (DMM). Two other murine tumors, the Meth A sarcoma in Balb/c mice and the L1210 leukemia in BDF1 mice, did not respond to treatment with normal syngeneic cells. In the L1210 system, tumor-promoting effects of fetal liver cells were demonstrated. The tumor inhibitory effects of normal lymph node cells against the Moloney lymphoma may be a virus-dependent phenomenon mediated through interferon and 'natural killer' cells. The experiments also showed the sensitivity of the Moloney lymphoma and the Meth A sarcoma to CY and DMM and the responsiveness of the L1210 leukemia to AAFC. (Author abstract) (25 Refs)

52. S PHASE-SPECIFIC SYNTHESIS OF DIHYDROFOLATE REDUCTASE IN CHINESE HAMSTER OVARY CELLS.

Mariani BD, Slate DL, Schimke RT
(c/o Schimke) Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305
Proc Natl Acad Sci USA; 78(8):4985-4989 1981

We investigated the cell cycle modulation of dihydrofolate reductase (DHFR; tetrahydrofolate dehydrogenase, 7,8-dihydroxyfolate: NADP+ oxidoreductase, EC 1.5.1.3) levels in methotrexate-resistant Chinese hamster ovary cells synchronized by mitotic selection. DNA content and DHFR concentration were analyzed throughout the cell cycle by standard biochemical techniques and by double fluorescence staining utilizing the fluorescence-activated cell sorter. We found an S phase-specific period of DHFR biosynthetic activity. Commencing within hr 2 of S phase and continuing throughout the duration of S phase, there is a 90% increase in DHFR specific activity. This results from an approx 2.5-fold increase in the level of DHFR, while total soluble protein increases 50% during the same period. This increase is the result of new synthesis of DHFR molecules initiated after the cell is physiologically committed to DNA replication. This increase in DHFR activity through S phase parallels the increasing rate of [3H]thymidine incorporation during the same interval. The max peak of DHFR activity is coincident with the max rate of DNA synthesis, both activities occurring during the bulk of DNA replication within the last stages of the 6.5-hr phase. (Author abstract) (26 Refs)

53. DIETARY SELENIUM INTAKE AND GROWTH OF THE MT-W9B TRANSPLANTABLE RAT MAMMARY TUMOR.

Ip C, Ip MM, Kim U
Dept. Breast Surgery, Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Lett; 14(1):101-107 1981

The effect of dietary selenium deficiency and supplementation on the growth of the transplantable MT-W9B mammary carcinoma in syngeneic Wistar-Furth female rats was investigated. The rats were fed a high fat diet (25% corn oil) supplemented with either less than 0.02 ppm, 0.1 ppm, or 2 ppm selenium. Selenium deficiency caused a drastic reduction in the activity of hepatic glutathione peroxidase, while excess selenium had little effect on its activity. Palpable tumors appeared earlier in the rats given less than 0.02 ppm or 0.1 ppm selenium, compared to those given 2 ppm. Dietary selenium at 2 ppm reduced the tumor wt by approx 50% compared to that in the 0.1 ppm group. No histological change in the tumors accompanied with the wt decrease. It is suggested that the inhibitory effect of selenium is selective, without inducing any wt loss or any recognizable toxicity in the animals. (25 Refs)

54. THE EFFECT OF FRACTIONATED VERSUS UNFRACTIONATED TOTAL BODY IRRADIATION ON THE GROWTH OF THE BN ACUTE MYELOCYTIC LEUKEMIA.

Hagenbeek A, Martens AC
Bone Marrow Transplant Unit., U.C.L.A. Sch. Medicine, Center for the Health Sciences, Los Angeles, CA, 90024
Int J Radiat Oncol Biol Phys; 7(8):1075-1079 1981

The quantitative and qualitative effects of various total body irradiation (TBI) regimens in a rat acute myelocytic leukemia model (BNML) which shares many characteristics with human acute myelocyitc leukemia, with emphasis on tumor load reduction are described. The results of high dose rate (HDR) acute, and HDR fractionated TBI, and the efficacy of low dose rate (LDR) continuous TBI are also reported. The most important determinants of HDR TBI efficacy were the total radiation dose and the dose delivered per fraction, and the time interval between the fractions. In the LDR TBI group, more leukemic cells were killed at higher radiation doses. However, at the time termination of treatment with 2,000 cGray, 50% of the rats had died. The remaining rats in this group as well as those treated with lower radiation doses all died from leukemia. Unfractionated TBI (900 cGray HDR) appeared to be one of the most effective regimens in terms of reducing the tumor load. However, approx half of the rats were killed by radiation-induced toxicity. The calculation of the log cell kill from the prolongation of median life span was found to be a valid method for determining the efficacy of TBI. (12 Refs)

55. FLOWCYTOMETRIC ANALYSIS OF THE EFFECT OF ANTITUMOR DRUGS USING A HUMAN NEUROBLASTOMA MODEL XENOGRAFTED INTO NUDE MICE.

Tsuchida Y, Yokomori K, Saito S, Takakura K, Yamamoto H, Nomura K
Dept. Pediatric Surgery, Faculty Medicine, Univ. Tokyo, Bunkyo-ku, Tokyo 113, Japan
Shoni Geka; 13(4):517-524 1981

Nude mice bearing human neuroblastoma in the sc tissue were injected ip with cis-platinum 10 mg/kg mouse wt, and changes in the cell cycle of the tumor specimens were studied with flow-cytometry. An increase in S phase cells and in G2 + M phase cells occurred 24-48 hr and 72 hr after the injection, respectively. Nude mice bearing human neuroblastoma were treated more effectively when epipodophyllotoxin was given 72 hr after the treatment with cis-platinum, or when adriamycin was given 36 hr after the treatment with cis-platinum, than when they were treated with the single agent alone. A significant increase in S phase was observed 7 days after subtotal resection of the tumor mass, and adriamycin given 7 days postoperatively was found more effective than that given 14 days postoperatively. (10 Refs) (In JPN)

56. POSTRADIATION DNA REPAIR IN MAMMALIAN CELLS AFTER COMBINED EXPOSURE TO HYPERTHERMIA, 8-BROMOCAFFEINE, AND ACTINOMYCIN D.

Rezvaia SP, Khanson KP
Central Res. Roentgenoradiological Inst., Leningrad, USSR
Radiobiologiia; 21(3):326-329 1981

The effect of combined exposure to hyperthermia, 8-bromocaffeine (BC), and actinomycin D (AD) on DNA repair was studied in irradiated (5,000 rads) LL cells. The level of double-stranded DNA after incubation with BC or AD at 41 C was significantly greater than that at 37 C. These findings indicate that hyperthermia does not enhance the inhibitory effect of BC and AD. (14 Refs) (In RUS)

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MARCH, 1982

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ANTITUMOR AGENT EFFICACY IN VIVO

1. DOXORUBICIN FOR TREATMENT OF CANINE LYMPHOSARCOMA AFTER DEVELOPMENT OF RESISTANCE TO COMBINATION CHEMOTHERAPY.

Calvert CA, Leifer CE

Dept. Small Animal Medicine, Coll. Veterinary Medicine, Univ. Georgia, Athens, GA, 30602

J Am Vet Med Assoc; 179(10):1011-1012 1981

Doxorubicin was used in 12 consecutive dogs with multicentric lymphosarcoma that had initially responded favorably to combination chemotherapy but, after a median of 30 wk of remission, had become refractory to the treatment modality. Complete remission was seen in four dogs, and no response was obtained in eight dogs. For the four dogs undergoing complete remission, approx remission times were 35 days, 128 days, 163 days, and 210 days. (Author abstract) (15 Refs)

2. EFFECT OF RETINOIDS ON THE B-16 MELANOTIC MELANOMA GROWTH (MEETING ABSTRACT).

Drewa G, Zbytniewski Z, Kancierz A

Medical Academy, Gdansk, Poland

Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

Inbred C57Bl mice were transplanted sc with B-16 melanotic melanoma. Two days after the tumor transplantation mice were injected ip once a day during ten following days with three retinoids; retinoic acid, retinol and retinal. All drugs were administered in the doses 10 or 50 mg/kg body wt. After 14 days mice were killed, the wt of tumors and the activity of arylsulphatases, acid phosphatase and beta-glucuronidase as well as melanins content were estimated in the tumor homogenate. It has been found that all retinoids tested inhibited the melanotic melanoma growth but the most effective was retinoic acid. (no Refs)

3. EFFECTS OF DAILY TREATMENT WITH A RADIOPROTECTOR WR-2721 ON EHRLICH'S ASCITES TUMORS IN MICE: SUPPRESSION OF TUMOR CELL GROWTH AND EARLIER DEATH OF TUMOR-BEARING MICE.

Ikebuchi M, Shinohara S, Kimura H, Morimoto K, Shima A, Aoyama T

Dept. Experimental Radiology, Shiga Univ. Medical Science, Shiga 520-21, Japan

J Radiat Res (Tokyo); 22(2):258-264 1981

The effects of daily administration of the radioprotector WR-2721 (S-2-[3-aminopropylamino]ethylphosphorothioic acid; 0, 1, and 5 mg/mouse ip) were determined in groups of 50 ICR/JCL female mice after inoculation of 5 x 10(7) Ehrlich ascites tumor cells ip. Groups of control mice received only the drug (0, 1, and 5 mg/kg). Tumor-inoculated mice treated with 5 mg WR-2721 exhibited reductions in body wt and number of ascitic cells. However, the survival curve for these mice deviated on approx day 11 from curve for mice receiving 0 or 1 mg/kg, with an increase in death rate. (6 Refs)

4. INFLUENCE OF ASCORBIC ACID AND COPPER ADMINISTRATION ON THE GROWTH AND DISSEMINATION OF B16 MELANOTIC MELANOMA (MEETING ABSTRACT).

Zbytniewski Z, Kancierz A, Drewa G

Medical Academy, Gdansk, Poland

Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

It is suggested that vitamin C acts as an anticancer agent. Addition of cupric ions enhances this antineoplastic effect in vitro and in vivo. The cytotoxic effect is due to gener ation of free radicals from the reaction between ascorbate and copper ions accumulated in melanotic tissue. In the present work C57BL mice were implanted sc with B16 melanotic melanoma into the tails. Seven days after tumor transplantation the animals were injected ip five x a wk during two wk as follows: 1) saline 0.1ml; 2) ascorbic acid 250 mg/kg in 0.1 ml; 3) CuSO4 5H2O in saline (2 mg of Cu++/kg); 4) ascorbate and Cu++ together in the same doses as group 2 and 3. The tails with tumors were amputated on 20th day and incidence of pulmonary metastases was estimated three wk later. The differences in mean tumor wt and incidence of pulmonary metastases between experimental and control groups were not statistically significant. (no Refs)

5. EFFECT OF ANTINEOPLASTIC AGENTS ON HUMAN BREAST CARCINOMA AND CHORIOEPITHELIOMA TRANSPLANTED INTO ATHYMIC NUDE MICE.

Revazova ES

All-Union Cancer Res. Center, Moscow, USSR

Vestn Akad Med Nauk SSSR; (9):79-83 1981

The effect of hormone therapy and chemotherapy on growth of transplanted human breast carcinoma and chorioepithelioma was studied in athymic BALB/c mice. Animals with tumor xenografts received single or repeated (5x) ip injections of dactinomycin (DM), methotrexate (MTX), vincristine, 5-fluorouracil, cyclophosphamide, adriamycin, or lomustine. Hormones (testosterone, cortisone, and hexestrol) were administered sc or po on day 4 after tumor transplantation. Chemotherapy failed to inhibit the growth of human breast carcinoma. Testosterone provided significant inhibition of breast carcinoma growth from day 10 of administration. DM and MTX were effected against xenografter chorioepithelioma; repeated administration provided more effective inhibition of chorioepithelioma growth than single administration. (7 Refs) (In RUS)

6. ANTITUMOR EFFECTS OF HYDROGEN PEROXIDE IN VIVO.

Nathan CF, Cohn ZA

Rockefeller Univ., New York, NY, 10021

J Exp Med; 154(5):1539-1553 1981

Antitumor activity of hydrogen peroxide (HP) against P338 lymphomas and P815 mastocytomas in female (BALB/c x DBA/2)F1 (CD2F1) mice was studied. Glucose oxidase was injected in free form (GO) or bound to latex beads (GOL). GOL suspension contained an av 5.8 x 10(10) beads/ml and produced an av 172 nanomoles H2O2/min. Binding of GO to beads prevented dispersal of GO from the injection sites. In mice injected with 10(6) P338 cells, 1 ml GOL increased survival time an av 3.2 days. Soluble GO produced no increase in survival. GOL was effective if injected up to 1 hr before P338 injection, but not if injected earlier. Exposure of mice to 100% O2 for 2-3.5 hr following GOL and P338 injection increased survival time an av 4.7 days. Supplemental glucose had no effect on survival time. Injection of beads bound with catalase abolished the antitumor effect of GOL, indicating that the effect of GOL was dependent on H2O2. Although no cures were obtained with injection of 10(6) P338 cells, cures were obtained with lower tumor cell doses. The LD50 of GOL against P815 tumors was 4.2x as great as for P338. P815 susceptibility to GOL was increased 5.5x by injection of 30 mg 1,3-bis(2-chloroethyl)-1-nitrosourea/kg body wt with GOL treatment. No toxic effects were noted for GOL, although preformed H2O2 was toxic. (42 Refs)

7. ANTITUMOR ACTIVITY OF BLEOMYCIN AGAINST MURINE SOLID TUMORS.

Bazhanov VS, Shorin VA
All-Union Res. Inst. Screening for New Antibiotics, Moscow, USSR
Antibiotiki; 26(9):694-696 1981

The therapeutic efficacy of bleomycin (BM) was studied in random-bred, CBA, and C3HA mice bearing transplanted solid tumors. A 90% inhibition of sarcoma 180, lymphosarcoma LIO-1, Harding-Passey melanoma, and cervical carcinoma CC-5 was achieved after sc BM administration at 28.0, 56.0, 20.0, and 120 mg/kg, respectively. A 90% inhibition of sarcoma 180 and lymphosarcoma LIO-1 after iv BM administration was achieved at 80.0 and 175.0 mg/kg, respectively. The LD50 for BM after sc administration was 30.0 mg/kg. (4 Refs) (In RUS)

ANTITUMOR AGENT EFFICACY IN VITRO

8. SELECTIVE ACTIVATION OF 5'-DEOXY-5-FLUOROURIDINE BY TUMOR CELLS AS A BASIS FOR AN IMPROVED THERAPEUTIC INDEX.

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Cancer Res; 41(12):4891-4894 1981

The intracellular metabolism of a new fluoropyrimidine, 5'-deoxy-5-fluorouridine (5'-dFUrd), was compared with the metabolism of 5-fluorouracil (FUra), 5-fluorouridine (FUrd), and 5-fluoro-2'-deoxyuridine (FdUrd) in freshly isolated bone marrow cells and Ehrlich ascites tumor cells. Following exposure to tumor cells, all four fluoropyrimidines were metabolized to identical products (i.e., FUra, 5-fluorouridine 5'-monophosphate, 5-fluorouridine 5'-dephosphate, 5-fluorouridine 5'-triphosphate, and 5-fluoro-2'-deoxyuridine 5'-monophosphate), all produced an incorporation of FUra into RNA (FUrd greater than FUra greater than FdUrd greater than 5'-dFUrd), and all completely inhibited thymidylate synthetase activity by 1 hr. However, in bone marrow cells, very different patterns were observed. 5'-dFUrd accumulated in the cells, but there were no measurable metabolism, no incorporation of FUra into RNA, and no inhibition of thymidylate synthetase activity. In contrast, both FUra and FUrd were metabolized and produced an incorporation of FUra into RNA (2.7 pmol FUra per mg RNA and 4.8 pmol FUra per mg RNA at 2 hr, respectively) in bone marrow. Only a minor inhibition of thymidylate synthetase activity was detected. FdUrd also was metabolized by bone marrow cells, produced a low level of FUra incorporation into RNA (0.23 pmol FUra per ug RNA at 2 hr), and produced a complete inhibition of thymidylate synthetase activity. Since 5'-dFUrd is not directly cytotoxic itself, its superior therapeutic index compared to other fluoropyrimidines may largely reflect the selective activation of 5'-dFUrd by sensitive tumor cells as opposed to bone marrow cells, which can activate FUra, FUrd, and FdUrd. (Author abstract) (17 Refs)

9. STUDY OF KILLING EFFECT OF RUBESCENSIN A AND B ON HUMAN LIVER CANCER CELL LINE BEL-7402.

Ge M, Ma Y, Zhang Z, Ma A, Liu H
Henan Cancer Inst., Henan Province, People's Republic of China
Yaoxue Tongbao; 16(5):6-9 1981

Rabdosia rubescens Hemsl, a plant widely distributed in China, has been recently demonstrated to be active against esophageal cancer. Its water and alcohol extracts have also shown significant cytotoxic effects on in vitro cancer cells (Hela cells and esophageal cancer) as well as animal tumors. The cytotoxic effects of its active principles (Rubescensin A and B) on a human hepatoma cell line (BEL-7402) are described and compared to those of 5-fluorouracil (5-FU). Results showed that both Rubescensin A and B had inhibitory effects on cell division, cell survival, cell proliferation and 3H-thymidine incorporation in BEL-7402 cells. Their effects were similar and dose-dependent and were generally stronger than those of 5-FU. The cell killing effects of Rubescensin A and B were about 2x those of 5-FU; the action of the former was rapid while that of the latter was delayed. This suggests that a combination of Rubescensin A and B and 5-FU would be more beneficial in cancer therapy and should be tested. (5 Refs) (In CHI)

10. EFFECTS OF PULSE AND CONTINUOUS INTRAVENOUS INFUSION OF CIS-DIAMMINEDICHLOROPLATINUM ON L1210 LEUKEMIA IN VIVO.

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Cancer Res; 41(12):4993-4996 1981

The in vivo effects of cis-diamminedichloroplatinum on L1210 leukemia were determined using DNA content distribution analysis by flow microfluorometry and pulse [3H]thymidine labeling indices. Pulse and continuous infusion schedules were investigated. Pulse cis-diamminedichloroplatinum (2 and 6 mg/kg) resulted in progression delay of cells in S and G2 phases and at higher doses (greater than or equal to 12 mg/kg) in G1 as well. Equivalent total doses administered by continuous infusion over 24 to 72 hr delayed cells in G2 with little apparent affect on G1 or S progression. A max survival of 70% increased life span over controls was achieved with a 12-mg/kg pulse. Infusion doses at least 2-fold higher were required to achieve similar increases in survival. Cell cycle changes did not predict for therapeutic benefit, suggesting that, at suboptimal doses, cells were capable of repair. The therapeutic index for both modes of administration was narrow. (Author abstract) (17 Refs)

11. ANTITUMOR AND ANTI-INTOXICATION ACTIVITIES OF FUMARIC ACID IN CULTURED CELLS.

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Dept. Toxicology and Experimental Pathology, Res. Inst. Chemobiodynamics, Chiba Univ., Inohana 1-8-1, Chiba 280, Japan

Gan; 72(5):777-782 1981

Fumaric acid, isolated as the active component of Capsella bursa-pastoris herbe for inhibiting the solid growth of Ehrlich tumor in mice, was found to reduce markedly the growth and viability of Ehrlich, MH134, and L1210 mouse tumor cells in culture at concentrations of 0.3 to approx 1.2 mg/ml. In contrast, fumaric acid at these concentrations in the culture medium had no deleterious effect on the monolayer development of mouse and chick embryo cells but exhibited activity to enhance the recovery of the cells from the toxic effects of mitomycin C, aflatoxin B1, N-methyl-N'-nitro-N-nitrosoguanidine, and potassium 1-methyl-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,4-dihydro 1,8-naphthyridine-3-carboxylate. (Author abstract) (19 Refs)

12. MULTICELLULAR TUMOUR SPHEROIDS FROM HUMAN BRAIN TUMORS. A MODEL FOR EXPERIMENTAL CHEMOTHERAPY IN VITRO? (MEETING ABSTRACT).

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Cell Biol Int Rep; 5(SupplA):42 1981

Multicellular tumor spheroids have been obtained from a range of fourteen primary and secondary human brain tumors. Tumor biopsies were minced, disaggregated with collagenase and the resultant cell suspension diluted to 5x10(5) cell/ml and inoculated into flasks coated with 0.5% agar. After approx one wk in static culture, single spheroids (mean vol 1.4 x 10(6) um(3)) were transferred into individual agar coated wells on a microtitration plate. At least 10 spheroids were used for each trial. They were exposed to graded concentrations of various chemotherapeutic agents (lomustine, Procarbazine, Vincristine, VM-26, Adriamycin, Mithramycin, L-asparaginase and Methotrexate) for 24 hr at 37 C. After treatment, drugs were removed, the spheroids washed and refed with fresh growth medium. The growth medium of treated and non-treated (control) spheroids was changed twice weekly throughout the assay. The spheroids were measured daily using an eye piece um for a 10 day period following drug removal and the growth delay calculated. Spheroids were also disaggregated after drug treatment and the colony forming efficiency in soft agar was determined. A dose dependant correlation was observed between both relative growth delay and cell survival with these cytotoxic agents. However, patterns of chemotherapeutic response were found to vary considerably between different tumor types and even between tumors of similar histopathology. The effects of corticosteroids, interferon and cyclic nucleotides on human tumor multicellular spheroids was also assessed using the same system. Spheroids produced from human brain tumors may be useful as models for the study of general biology as well as a model for experimental in vitro chemosensitivity. (no Refs)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

13. EFFECTS OF ALPHA-DIFLUOROMETHYLORNITHINE ALONE AND COMBINED WITH ADRIAMYCIN OR VINDESINE ON L1210 LEUKEMIA IN MICE, EMT6 SOLID TUMORS IN MICE, AND SOLID TUMORS INDUCED BY INJECTION OF HEPATOMA TISSUE CULTURE CELLS IN RATS.

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Cancer Res; 41(12):5158-5161 1981

The effects of alpha-difluoromethylornithine (DFMO; RMI 71782) in combination with vindesine or Adriamycin were investigated in three different animal tumor models. When given in a concentration of 2% in drinking water to C57BL/6 x DBA/2 F1 mice inoculated ip with L1210 leukemia cells, DFMO prolonged the survival time 1.2-fold. Treatment with vindesine (0.1 mg/kg/wk ip or Adriamycin (2.5 mg/kg/wk ip) increased the mean survival time 1.4-and 2.3-fold, respectively. DFMO with vindesine doubled survival time, while DFMO with Adriamycin increased it 3.5-fold and yielded 30% long-term survivors. The growth of solid tumors induced in Buffalo rats by im injection of hepatoma tissue culture cells was inhibited 65% after 2 wk of DFMO treatment. Similar inhibition of growth could be achieved by weekly ip injections of vindesine (0.2 mg/kg) or Adriamycin (2.5 mg/kg). When the same doses of these drugs were administered in combination with DFMO, the growth of this hepatoma was completely arrested. Combined treatment of BALB/c mice bearing sc solid EMT6 tumors with DFMO and Adriamycin or vindesine also resulted in enhanced inhibition of tumor growth compared to single-drug therapy. These results indicate that combination of DFMO with vindesine or Adriamycin is an effective approach to the treatment of several animal cancers. (Author abstract) (15 Refs)

14. CAIN'S QUINOLINIUM (NSC 176319): PROTECTION OF MURINE L1210 LEUKEMIA CELLS AND BONE MARROW PROGENITOR CELLS AGAINST MECHLORETHAMINE CYTOTOXICITY AND ITS APPLICATION TO COMBINATION CHEMOTHERAPY.

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Res Commun Chem Pathol Pharmacol; 34(1):97-104 1981

Cain's Quinolinium; quinolinium, 6-amino-1-methyl-4[[[[[[(1-methyl-pyridinium-4 yl)amino]phenyl]amino]carbonyl] phenyl]amino] (NSC 176319), is a chemotherapeutic agent, which is equally cytotoxic in vitro to both murine L1210 leukemia cells and bone marrow progenitor cells. At non-toxic concentrations it equally protects L1210 cells and bone marrow progenitor cells against mechlorethamine cytotoxicity. However, treatment of murine L1210 leukemia bearing mice with the combination of Cain's Quinolinium and mechlorethamine at a mole ratio of 1:1 resulted in 100% long term survivors compared to 50% with Cain's Quinolinium alone or 0% with mechlorethamine alone. (Author abstract) (10 Refs)

15. EFFECT OF PROLONGED EXPOSURE OF HELA S3 CELLS TO LOW CONCENTRATIONS OF MISONIDAZOLE.

Ohizumi Y, Shibata C, Maezawa H, Ushiro S, Mori T
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Gan; 72(5):717-722 1981

The cytotoxic and radiosensitizing effects of low concentrations of misonidazole were examined by measurement of the colony-forming ability and growth of HeLa S3 cells. Under hypoxic conditions, cytotoxicity depended on the misonidazole concentration and the exposure time. After 24 hr exposure, the surviving fraction of cells treated with 0.1 mM misonidazole decreased to 0.2. The ability of cells to adhere to the growth surface of plastic dishes was reduced by 0.1 mM misonidazole upon 24 hr hypoxia and this effect persisted even during subsequent euoxia, irrespective of whether the drug was removed from the original growth medium. The growth of aerobic cells was not affected when 0.1 mM misonidazole-containing medium, obtained from the hypoxia-treated dishes, was applied, nor when these cells were exposed for 72 hr to freshly prepared 1.0 mM misonidazole. Upon 24 hr exposure, 0.1 mM misonidazole exerted no obvious radiosensitizing effect on hypoxic cells. Based on these results, it is suggested that continuous administration of low doses of misonidazole may be efficacious as a specific chemotherapeutic in the treatment of hypoxic cells in tumor tissue. (Author abstract) (16 Refs)

16. ENHANCEMENT OF THE ANTITUMOR EFFECT OF 6-MERCAPTOPURINE BY VITAMIN A.

Akiyama S, Masuda A, Tabuki T, Kuwano M, Komiyama S
Dept. Biochemistry, Oita Medical Sch., Hazama-cho, Oita 879-56, Japan
Gan; 72(5):742-746 1981

The inhibition of the growth of HeLa cells in culture by 6-mercaptopurine was greatly enhanced in combination with retinol, retinal or retinol acetate, but not in combination with retinoic acid or retinol palmitate. The antitumor effect of retinol palmitate combined with 6-mercaptopurine was examined in BDF1 mice with L1210 leukemia. The blood level of retinol, a strong potentiator of 6-mercaptopurine among vitamin A compounds, was increased in BDF1 mice after retinol palmitate injection. Retinol palmitate was found to enhance the antitumor effect of 6-mercaptopurine against murine L1210 leukemia to a significant extent (69% increase in life span). (Author abstract) (19 Refs)

17. THE EFFECTIVENESS OF CARMINOMYCIN IN COMBINATION WITH DIBROMODULCITOL ON HUMAN TUMOR CELLS IN VITRO.

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Arch Geschwulstforsch; 51(6):497-502 1981

The effects of the antineoplastic agents carminomycin (CRM) and dibromodulcitol (DBD) were studied individually and in combination. Morphologically and chemically characterized human mesothelioma cells from the 25-30th passage were cultured. After 24 hr fresh culture medium with or without CRM and/or DBD was added. The cytostatic effects of CRM and DBD were determined by measuring the uptake of [3H]thymidine added 48 hr after addition of the agents tested. CRM had a greater effect in proportion to concentration than DBD. CRM at a concentration of 1.2 x 10(-8) M produced a 30.6% +-9.3 % reduction in thymidine uptake compared with controls. DBD produced a reduction of 35.3% +-18.3% at a concentration of 3.9 x 10(-6) M. CRM and DBD in combination had a synergistic effect in 14 of 27 experiments. However, statistical evaluation of total results did not confirm this. Adding CRM and DBD at different times did not change the results obtained from simultaneous addition. (15 Refs) (In GER)

18. THERAPEUTIC EFFECTS OF ACNU AND RADIATION ON RAT GLIOMA.

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Neurol Surg; 9(3):257-265 1981

Effects of 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2 chloroethyl)-3-nitrosourea hydrochloride (ACNU) and/or radiation on rat glioma clone-6 cells (RGs) were investigated. Using an in vitro colony formation assay, addition of 100 ug/ml of ACNU to a RG culture medium was shown to result in 50% survival of cells at 15 min and a biphasic decrease of surviving cells. Dose-survival curves for ACNU indicated repair of sublethal damage at 0-25 ug/ml, and dose-survival curves for x-rays showed Dq = 490 rads and Do = 220 rads. The optimum time interval for administration of 600 rads x-rays after giving 10 ug/ml of ACNU was greater than 3 hr. Rats with sc transplanted RGs were irradiated with 1,000 rads of x-rays 3-12 hr after administration of 10 ug/ml of ACNU when the RG tumors were 2,000-4,000 cubic mm; synergistic increase in doubling time was observed, but no synergistic increase in the life span of the rats was observed. The findings indicated that combinations of ACNU and radiation have a synergistic cell-killing effect on the growth of RG tumors but also suggested that the normal tissues may have been effected as well. (26 Refs) (In JPN)

19. ADVANCED NON-HODGKIN'S LYMPHOMA IN ADULTS. CYTOSTATIC CHEMOTHERAPY.

Meuthen I, Modder B
Medizinische Poliklinik, Universitat Koln, Joseph-Stelzmann-Strasse 9, D-5000 Koln 41, W. Germany
Med Welt; 32(41):1545-1547 1981

The chemotherapy of advanced non-Hodgkin's lymphoma (NHL) in adults is reviewed. Monotherapy with Leukeran, cyclophosphamide (CP), Natulan, or vincristine (VCR), as well as polychemotherap y with CP, VCR, and prednisone (PR) are most effective in low-grade NHL. However, the survival is not prolonged by polychemotherapy compared with single-agent chemotherapy, even though the complete remission rate is 15% higher after polychemotherapy. Therefore, the use of aggressive polychemotherapy protocols may not be justified. Polychemotherapy with the combination of bleomycin (BL), adriamycin (ADR), VCR, and PR is the high-grade NHL, but CP-VCR-methotrexate-ADR, CP-adriablastin-VCR-PR, CP-VCR-procarbazine (PRO), and CP-VCR-PRO-PR are also effective. Maintenance therapy during complete remission may be useful in low-grade cases, but it fails to prolong the survival and the recurrence-free period in high-grade NHL. (15 Refs) (In GER)

20. CELL SURVIVAL RECOVERY KINETICS IN THE KHT SARCOMA FOLLOWING TREATMENT WITH FIVE ALKYLATING AGENTS AND MISONIDAZOLE (MEETING ABSTRACT).

Siemann DW, Mulcahy RT
Experimental Therapeutics Division, and Departments of Radiology,, Radiation Biology and Biophysics University of Rochester Cancer Center, 601 Elmwood Avenue, Box 704, Rochester, NY, 14642
Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17-20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

We have evaluated the effects of combining the radiosensitizer misonidazole (MISO) with alkylating agents 1-(2-chloroethyl)-3-cyclohexyl-l-nitrosourea (CCNU), 1,3-bis(2-chloroethyl)-l-nitrosourea (BCNU), cyclophosphamide (Cy), phenylalanine mustard (L-PAM) and 2-[3-(2-chloroethyl)-3-nitrosoureido]-D-glucopyranose (chlorozotozin; CHLZ). When clonogenic cell survival was assessed 24 hr after treatment, the addition of 1.0 mg/g MISO led to dose modification factors of 2.4, 1.8, 1.3, 1.4, 1.0 for CCNU, BCNU, Cy, L-PAM, and CHLZ respectively. C3H mice were injected im in the hind limbs with KHT sarcoma cells and treated when the tumors reached a size of approx 0.2-0.4g. Single 7.5, 10, 50, 5, and 20 mg/kg doses of CCNU, BCNU, Cy, L-PAM, and CHLZ respectively were chosen for study in order to obtain approx the same level of cell kill with each treatment. These doses of the chemotherapeutic agents were administered either alone or in simultaneous combination with a 1.0 mg/g dose of the radiosensitizer. Tumors were excised at 1, 2, 4, 8, 16, and 24 hr after drug injection. Clonogenic cell survival at these time points was assessed using an in vivo to in vitro excission assay. Following treatment with each of the chemotherapeutic agents, tumor cell survival reached a minimum at approx 2-8 hr. Subsequently cell survival increased with time by a factor of approx 10-100 for CCNU and BCNU and approx 2-10 for Cy, L-PAM, and CHLZ. The addition of MISO apparently altered little the clonogenic cell survival observed at early times after treatment. However, in animals treated with the chemotherapeutic agent plus the sensitizer, cell survival recovery was impaired. This effect was particularly marked when the nitrosoureas CCNU and BCNU were used in combination with MISO. For example, 24 hr after treatment with CCNU plus MISO, tumor cell survival was a factor of approx 20-50 lower than observed in tumors of mice given only CCNU. (no Refs)

21. RESPONSE TO SINGLE AGENT AND COMBINATION CHEMOTHERAPY OF A HUMAN PANCREATIC DUCTAL ANDENOCARCINOMA GROWN IN THE NUDE MOUSE. LETHAL SYNERGISTIC EFFECT OF CIS-DICHLORODIAMMINEPLATINUM, CYTOSINE ARABINOSIDE AND CAFFEINE (MEETING ABSTRACT).

Kyriazis AP, Kyriazis AA, Yagoda A
University of Cincinnati Medical Center, Cincinnati, OH, 45267
Newsletter Natl Pancreas Cancer Project; VI(2):31 1981

Concurrent administration of cis-Dichlorodiammineplatinum (II), cytosine arabinoside and caffeine displayed a dramatic synergistic antitumor effect against human pancreatic ductal adenocarcinoma line capan-1 grown in the nude mouse. Cisplatin alone significantly decreased tumor growth, but the addition of cytosine arabinoside was not superior to that which could be obtained with cisplatin alone. While 5-fluorouracil and cyclophosphamide singularly were ineffective, the combination of both drugs - depending upon timing and sequence of administration - significantly affected tumor growth. Thus, in combination chemotherapy, the timing and sequence of drug administration is of paramount importance in determining tumor response, particularly in the nude mouse. (no Refs)

22. THE ENHANCEMENT OF EFFECT OF CHEMOTHERAPEUTIC DRUGS BY RADIOSENSITISERS (MEETING ABSTRACT).

Martin WM, McNally NJ
Gray Laboratory of the Cancer Research Campaign, Mount Vernon, Hospital Northwood, Middlesex, England
Br J Cancer; 43(5):729 1981

Cells from sc tumors of the culture-adapted sarcoma, WHFIB, were found to exhibit repair of potentially lethal damage (PLD) after treatment by cyclophosphamide (CY). Misonidazole (MISO) given 1 hr prior to CY inhibited this PLD repair and caused potentiation of Cy cytotoxicity, which was more marked at 24 hr than 4 hr after CY injection. One mg/g MISO caused a dose-modifying factor (DMF) of 2.1 with this system. Comparable effects were also found using the regrowth-delay assay. Other 2-nitroimidazole radiosensitizers also potentiated the action of CY. MISO given 6 hr before CY, simulataneously, or even 2 hr after, caused significant potentiation of cytotoxicity, but MISO given 1 hr before CY produced the optimal effect. There was a linear relationship between sensitizer dose and the regrowth delay following combined treatment. With melphalan, 1 mg/g MISO caused a DMF of 2.5. Two mm WHFIB lung tumors did not exhibit repair of PLD after CY and also showed less potentiation of CY cytotoxicity by MISO than sc tumors. Normal-tissue effects have been encouraging: the CY-induced LD50/60 was altered by less than 10% by combination with 1 mg/g MISO; and 1 mg/g MISO caused no significant increase in leukopenia with therapeutic doses of CY. (no Refs)

23. INHIBITORY EFFECTS OF ANTI-NEOPLASTIC PLATINUM COMPLEXES ON DNA AND RNA POLYMERASES (MEETING ABSTRACT).

Kohl HH, Miller DL
Chemistry Department, Auburn University, Auburn, AL, 36849
Clin Chem; 27(6):1066 1981

The present work studies the inhibitory actions of cis-diaminedichloroplatinum II (cis-DDP), trans-diaminedichloroplatinum II (trans-DDP) and other more recently synthesized platinum complexes on both DNA and DNA-dependent RNA polymerases. Soluble and purified enzymes from Escherichia coli were studied in the presence of either a calf-thymus DNA template or Poly (dA-dT). We have also studied a completely mammalian transcription system (intact rat liver nuclei) in a DNA-dependent RNA polymerase assay. Measurements of RNA transcription were made using radioactive guanosine triphosphate while those of DNA synthesis utilized tritiated thymidine triphosphate. Incorporation of radioactivity was measured by counting glass fiber filters using liquid scintillation. Our data indicates that the trans-DDP is far more potent than cis-DDP in inhibiting RNA transcription. Ninety percent inhibition was seen using 10 uM trans-DDP while less than 5% inhibition was seen using cis-DDP. The inhibitions of RNA transcription appear to be due to effects on the polymerase enzyme rather than to effects on the DNA template. DNA synthesis, however, appeared to be inhibited by effects on both the enzyme and the nucleic acid template. (no Refs)

24. THE COMBINED EFFECT OF BLEOMYCIN AND HYPERTHERMIA ON THE ADENOCARCINOMA 284 OF THE C3H MOUSE.

von Szczepanski L, Trott KR
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Eur J Cancer Clin Oncol; 17(9):997-1000 1981

Isogeneic adenocarcinomas of female C3H mice were treated with bleomycin and local hyperthermia and tumor regrowth delay was measured. Hyperthermia had a synergistic effect on the drug induced growth delay. Heating to 44.5 C for 20 min, 30 min after bleomycin, increased the slope of the dose response curve by a factor of 2.7 whereas the same heat treatment given 30 min before the drug increased the slope of the dose response curve only by a factor of 1.5. (Author abstract) (16 Refs)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

25. CHANGES IN THE CONCENTRATION OF HEMATOPOIETIC STEM CELLS, ERYTHROCYTES AND LEUKOCYTES DURING HEPATOMA GROWTH AND AFTER TREATMENT WITH ANTINEOPLASTIC AGENT.

Sadovnikova IP, Obukhova LK
Inst. Chemical Physics, Moscow, USSR
Izv Akad Nauk SSSR [Biol]; (5):781-785 1981

The effect of tumor growth and treatment with antineoplastic agents on hematopoietic stem cells was studied in female C3HA mice with transplanted hepatoma 22a. On days 3, 7, 11, and 15 after tumor transplantation, animals received ip injections of diazane (1,2-bis-diazoacetylethane) at 150 mg/kg. Progressive tumor growth was associated with development of erythropenia and leukocytosis. There was an increase of the concentration of colony-forming units (CFU) in the bone marrow and increase of CFU migration to the spleen. Diazane administration reduced tumor size and normalized WBC count. Diazane decreased CFU concentration on days 8 and 12 after tumor transplantation, but both the CFU count and CFU migration in treated tumor-bearing animals exceeded those in intact controls. (16 Refs) (In RUS)

26. PREVENTION OF DOXORUBICIN CARDIAC TOXICITY IN THE MOUSE BY N-ACETYLCYSTEINE.

Doroshow JH, Locker GY, Ifrim I, Myers CE
Pharmacology Section, Dept. Medical Oncology, City of Hope Natl. Medical Center, Duarte, CA, 91010
J Clin Invest; 68(4):1053-1064 1981

This study was undertaken to investigate the effect of exogenous sulfhydryl compound administration on the toxicity of doxorubicin in mice. Pretreatment of CDF1 mice with a pharmacologic dose (2,000 mg/kg) of n-acetyl-l-cysteine 1 hr before doxorubicin (20 mg/kg, ip) decreased lethality from 100% (n = 44) to 37.7% (n = 53), p less than 0.001. Variation in the timing and dose of n-acetylcysteine significantly diminished its protective activity. Pretreatment with n-acetylcysteine also significantly reduced long-term mortality in animals receiving multiple doses of doxorubicin; 10 wk after the third of three doxorubicin doses (5 mg/kg, ip) administered at 2-wk intervals, survival in the n-acetylcysteine pretreated group was 51.4% (n = 35) compared with 16.7% (n = 30) for animals receiving saline before doxorubicin, p less than 0.01. In this experiment, n-acetylcysteine pretreatment also diminished doxorubicin-related losses in total body wt and heart wet wt by 55.2% (p less than 0.05), and 60.9% (p less than 0.02), respectively, compared with animals pretreated with saline. N-acetylcysteine pretreatment also ablated electron microscopic evidence of doxorubicin cardiomyopathy without alleviating morphological features of its toxic effects on the liver or small intestinal mucosa. The cardioprotective action of n-acetylcysteine may be partially explained by the 429 +-60% increase in cardiac nonprotein sulfhydryl content (p less than 0.01) that was measured 1 hr after n-acetylcysteine administration; nonprotein sulfhydryl concentration in the liver at the same time was insignificantly different from control levels. Treatment with n-acetylcysteine also increased the nonprotein sulfhydryl content of P388 leukemia cells nearly threefold; however, it did not alter the chemotherapeutic activity of doxorubicin against this murine tumor. Whereas n-acetylcysteine blocked doxorubicin cardiac toxicity, it did not affect the uptake or metabolism of doxorubicin in the heart or liver. These results suggest that the concentration of free sulfhydryl groups in the heart may play a role in the development of doxorubicin cardiac toxicity and that augmenting cardiac nonprotein sulfhydryl group content with n-acetylcysteine may provide a means to enhance the chemotherapeutic index of doxorubicin. (Author abstract) (44 Refs)

27. TOXICOLOGICAL EVALUATION OF CARMINOMYCIN - AN ANTINEOPLASTIC ANTHRACYCLINE ANTIBIOTIC (MEETING ABSTRACT).

Buroker RA, Johnson DF, Madissoo H
Department of Toxicology, Bristol Laboratories, Syracuse, NY
Toxicologist; 1(1):130 1981

Carminomycin, an anthracycline antibiotic discovered in the Soviet Union, possesses antitumor activity and is chemically related to adriamycin and daunorubicin. The toxic effects of carminomycin observed in single-dose toxicology studies in mice iv (1.5-4.5 mg/kg) and po (6.3-17.4 mg/kg), rats iv (1.0-3.5 mg/kg), dogs iv (0.05-1.0 mg/kg) and po (0.8-4.0 mg/kg), Rhesus monkeys po (2.0-12.0 mg/kg); and in multiple-dose studies in dogs iv (18 doses 0.03-0.25 mg/kg, 2X/wk) and rats sc (9 doses 0.5-2.0 mg/kg, 3X/wk), were dose-related and primarily manifested as suppression of hematopoesis. The changes observed consisted of reduction in numbers of bone marrow cells of the myeloid and erythroid series, and of lymphoid and/or reticuloendothelial cells. Other toxicities observed included nephrotoxicity, gastrointestinal toxicity, decreased spermatogenesis, decrease in size and activity of the prostate and seminal vesicles, and ovarian alterations. In general, these toxicities were reversible in surviving animals during 6 wk to 4 mo recovery periods. The LD50 values in mice iv and po were determined as 2.05 and 12.6 mg/kg respectively. Cardioxicity, similar to that seen with adriamycin (13 weekly doses of 2.0 mg/kg) was not observed with carcinomycin (13 weekly doses of 1.0 mg/kg). (2 Refs)

28. A REGULATORY MECHANISM FOR THE NUMBER OF PLURIPOTENTIAL HAEMOPOIETIC PROGENITOR CELLS IN MICE.

Blackett NM, Botnick LE
Biology Div., Inst. Cancer Res., Fulham Road, London S.W.3, England
Blood Cells; 7(2):417-426 1981

Marked changes in pattern of regeneration of hemopoietic progenitor cells (CFU-S) were found as the result of altering time interval between im administration of cytotoxic agents (cyclophosphamide, 200 mg/kg; cytosine arabinoside, 200 mg/kg; 5-fluorouracil, 100 mg/kg) to mice and whole-body irradiation. Results suggest a negative feedback control for CFU-S with an appreciable time delay. Certain morphological studies of cells are reported which indicate a substance is secreted by these cells that controls the number but not the proliferation rate of CFU-S. (10 Refs)

29. CARCINOGENIC EFFECTS OF CHEMOTHERAPEUTIC AGENTS IN EXPERIMENTAL ANIMALS (MEETING ABSTRACT).

Weisburger EK
National Cancer Institute, Bethesda, MD, 20205
Long Term Normal Tissue Effects of Cancer Treatment, April 13-15, 1981, Bethesda, Maryland Committee for Radiation Oncology Studies; 1981

Tests for possible carcinogenicity have usually not been considered because of the time element and the fact that the risk-benefit ratio is generally in favor of using chemotherapeutic agents. However, clinicians employing these drugs should be aware of the possible induction of a second neoplasm by the chemotherapeutic agents. Support for this thesis comes from carcinogenicity studies in rats and mice of various drugs used in chemotherapy of neoplastic and certain other chronic diseases. The test protocol involved ip injection into Sprague-Dawley rats or Swiss-Webster mice three x weekly at two dose levels for six mo followed by one yr of observation. Drugs which significantly increased the tumor rate or induced types of tumors not seen in controls included: actinomycin D, chlorambucil, dacarbazine, melphalan, mitomycin C, procarbazine and streptozotocin. Cytoxan increased tumors of the lung in mice and of the mammary gland in rats; there was also an increase in bladder papillomas in male mice. Drugs which increased tumor incidence 2-to 3-fold over that in controls included: carmustine (male mice); imidazole mustard (female mice); lomustine (female mice); cytoxal alcohol (male and female mice); 6-mercaptopurine (male and female mice); and o-merphalan (female mice). Various other drugs including cytosine arabinoside, azathioprine, methotrexate, prednisone, vinblastine and vincristine led to a tumor incidence like that of controls. Various drug combinations generally did not increase tumor rates over those in controls. (no Refs)

30. AMYGDALIN (LAETRILE) AND PRUNASIN BETA-GLUCOSIDASES: DISTRIBUTION IN GERM-FREE RAT AND IN HUMAN TUMOR TISSUE.

Newmark J, Brady RO, Grimley PM, Gal AE, Waller SG, Thistlethwaite JR
Developmental and Metabolic Neurology Branch, Natl. Inst. Neurological and Communicative Disorders and Stroke, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 78(10):6513-6516 1981

Amygdalin, the gentiobioside derivative of mandelonitrile commonly referred to as Laetrile, is presently under intensive investigation as a potential cancer chemotherapeutic agent. Because of this interest, we investigated the activity of beta-glucosidases that cleave glucose from amygdalin and from prunasin (mandelonitrile monoglucoside) in tissues from germ-free rats and in normal and neoplastic human tissues. Rat and human small intestinal mucosa contain high levels of activity of glucosidases that act on both of these cyanogenic glucosides. Release of glucose from these compounds was not detected in any of the human neoplastic tissues examined in the present study. These observations are consist ent with reports of cyanide toxicity through the oral use of amygdalin or prunasin and pose serious questions concerning the alleged tumoricidal effect of amygdalin. (Author abstract) (22 Refs)

31. TREATMENT OF MURINE TUMORS WITH LETHAL DOSES OF DIMETHYLMYLERAN AND AUTOLOGOUS BONE MARROW.

Floersheim GL
Lab. Transplantation Biology, Dept. Res., Dept. Surgery, Zentrum fur Lehre und Forschung, Kantonsspital, Hebelstrasse 20, CH-4031 Basel, Switzerland
Eur J Cancer Clin Oncol; 17(8):905-912 1981

A murine model for autologous bone marrow transplantation is presented. Up to 90% of CBA and Balb/c mice survived a lethal dose of dimethylmyleran (DMM) if they were infused iv with autologous marrow cells removed prior to the injection of the drug. Autologous or syngeneic hemopoietic cells afforded equivalent protection. A significant proportion of CBA mice carrying the syngeneic YBA lymphoma and of Balb/c mice inoculated with the syngeneic Meth A sarcoma enjoyed lasting tumor-free remissions after treatment with a single lethal dose of DMM and autologous marrow. Sublethal doses of DMM failed to eradicate the tumors. Although curative tumor chemotherapy with autologous marrow was demonstrated, potential difficulties consist of the increased susceptibility of tumor bearing mice to the cytotoxic drug and the contamination of the marrow as early as 1 day after ip tumor inoculation. (Author abstract) (22 Refs)

PHARMACOKINETICS OF ANTITUMOR AGENTS

32. PHARMACOKINETIC STUDIES ON 3H-N-HYDROXYCANTHARIDINIMIDE.

Ho S, Wu L, Lu P
Tianjin Inst. Materia Medica, Tianjin, People's Republic of China
Yaoxue Xuebao; 16(5):328-333 1981

Hydroxycantharidinimide is a new agent that has antitumor activities similar to those of cantharidin but is approx 500x less toxic than the latter. A pharmacokinetic study of the agent in rats is described. Results obtained following iv administration were found to fit a two-compartment open model with first order elimination, whereas those obtained following oral administration were found to fit a one-compartment open model with first order absorption and elimination. (10 Refs) (In CHI)

33. SYNTHESIS OF 5-FLUOROURACIL-ALBUMIN CONJUGATE AND ANTITUMOR ACTIVITY OF THE PHAGOCYTIZED CONJUGATE.

Bukhman VM, Brusentsov NA, Kikot' BS, Volodin IuIu, Chertkova AI, Preobrazhenskaia MN
All-Union Cancer Res. Center, Moscow, USSR
Khim Farm Zh; 15(8):58-65 1981

The antitumor activity of a newly synthesized conjugate of macroaggregate of human serum albumin (maHSA) and 5-fluorouracil (5-FU) was studied in B6D2F1 mice bearing Rauscher leukemia and in CBAB6F1 mice bearing solid hepatoma H-2-73. The iv administration of the maHSA-5-FU conjugate at 8-90 mg/kg reduced spleen and liver wt in both the Rauscher leukemic and solid hepatoma mice. These findings indicated that maHSA can be used as a carrier which delivers cytostatics to the organs of the mononuclear phagocytic system. (17 Refs) (In RUS)

34. PHARMACOKINETIC ASPECTS OF INTERACTIONS BETWEEN NITROIMIDAZOLES AND OTHER DRUGS (MEETING ABSTRACT).

Workman P
MRC Clinical Oncology and Radiotherapeutics Unit, Hills Road, Cambridge CB2 2QH, England
Br J Radiol; 54(640):369 1981

We have been interested in the pharmacokinetics of interactions between nitroimidazoles and other drugs, (1) as experimental probes and (2) as possible means of reducing neurotoxicity. The hepatic microsomal enzyme-inducers phenobarbitone and phenytoin increased the clearance of misonidazole and lipophilic analogues through more rapid metabolism, but did not affect the pharmacokinetics of hydrophilic analogues such as desmethylmisonidazole. When evaluated as potentially superior enzyme inducers, antipyrine was less effective than phenobarbitone in mice whereas pregnenolone-16 alpha-carbonitrile (SC-4674, Searle) was about equally effective. Dexamethasone had no effect on misonidazole metabolism in mice but in some circumstances reduced misonidazole brain levels. Dexamethasone or inducers of oxidative metabolism such as phenobarbitone and phenytoin may reduce misonidazole neurotoxicity. Alternatively, if nitroreduction is involved in the toxic mechanism, inhibition of this pathway might be effective. The enzyme xanthine oxidase can act as a nitroreductase and is inhibited by allopurinol. Interaction between allopurinol and misonidazole in mice was reported recently by Raleigh et al. We have shown that allopurinol pretreatment did not change the pharmacokinetics of misonidazole or desmethylmisonidazole in mice. Given as a single dose 30-60 min before, allopurinol had little or no effect on the clearance of misonidazole or the more lipophilic analogue Ro 07-0913. In contrast, the clearance of the more hydrophilic desmethylmisonidazole and SR-2508 was considerably reduced. (no Refs)

35. PHARMACOKINETICS OF VINBLASTINE IN RAT BLOOD PLASMA AND TUMOUR TISSUE DETERMINED BY A BIOLOGICAL METHOD USING FLOW CYTOFLUORIMETRY.

Kipp JB, Barendsen GW
Lab. Radiobiology, Univ. Amsterdam, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
Eur J Cancer Clin Oncol; 17(8):867-873 1981

For the optimal use of vinblastine as an antineoplastic agent, knowledge of the pharmacokinetic distribution in blood plasma and tumor tissue is necessary. A method is presented for the determination of mitotic inhibitory activity of vinblastine and its metabolites, extracted from tissue samples. With this method concentrations as low as 0.005 mg/l which are biologically active can be reproducibly determined. The method has been applied to follow the concentration of vinblastine in blood plasma and tumor tissue after injection of 1.5 mg of vinblastine/kg body wt in WAG/Rij rats with a R-1,M tumor of 0.3-1. 0 g growing in the flank. The high concentration in plasma immediately after iv injection decreases quickly within 24 hr to the minimal detectable concentration in plasma of 0.01 mg/l. Although after ip injection the concentration in plasma is lower initially, at 24 hr it tends to be higher than after iv injection. In tumor tissue the max concentration is reached at 6 hr after iv injection (3.0 mg/kg) and at 12 hr after ip injection (0.6 mg/kg). From 12 hr after ip injection the concentration remains constant during 2-3 days while after iv injection a slow decrease is observed. These pharmacokinetic data are compared with the changes of cell proliferation kinetics in the tumor induced by vinblastine. The finding that after iv injection the max concentration in tumor tissue is higher and is reached earlier than after ip injection correlates well with the higher degree of accumulation of cells in mitosis. (Author abstract) (13 Refs)

36. STUDIES ON THE FATE OF TEGAFUR-URACIL (1:4) COMBINATION (UFT), AN ANTITUMOR AGENT. IV. METABOLISM IN RATS AFTER REPEATED ORAL ADMINISTRATION.

Kawaguchi Y, Nagayama S, Masuda H, Yasuda A
Res. Lab., Taiho Pharmaceutical Co. Ltd., Kawauchi-cho, Tokushima-shi, Tokushima 771-01, Japan
Oyo Yakuri; 21(3):411-416 1981

After repeated po administration of UFT [1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) plus uracil, 1:4] to tumor-bearing rats for a wk, the levels of tegafur and alpha-fluoro-beta-alanine in the blood and tissues were the same as in the group given a single dose. In the group given UFT repeatedly, the levels of 5-fluorouracil and alpha-fluoro-beta-ureidopropionic acid in almost all tissues tended to increase more than those in the group given the drug singly. The levels of 5-fluorouridine and fluoronucleotides in the tumor tissues, the incorporation of radioactivity into the acid insoluble fraction of tumors, and the levels of unknown metabolites in the liver, kidney, and small intestine increased more in the group given UFT repeatedly than in the group given a single dose. There was no significant difference between the ratios of the main metabolites excreted in the urine in the two groups. The cytochrome content and the activities of microsomal drug-metabolizing enzymes in the liver were not influenced by the repeated administration of UFT at a dose of 48.6 (15 as tegafur) mg/kg/day, but a higher dose of tegafur (90 mg/kg/day) than that of tegafur in the UFT significantly increased them. There was no qualitative difference in the tissue distribution in the groups given UFT and tegafur repeatedly. (9 Refs) (In JPN)

37. PHARMACOKINETICS OF A NEW WATER-SOLUBLE NITROSOUREA, 1-(2-CHLOROETHYL)-3-(METHYL-ALPHA-D-GLUCOPYRANOSE-6-YL) 1-NITROSOUREA (MCNU) IN BRAIN TUMORS.

Harada K, Kiya K, Kobayashi M, Takeda T, Mukada K, Uozumi T
Dept. Neurosurgery, Hiroshima Univ., Sch. Medicine, Kasumi, Hiroshima 734, Japan
Gan To Kagaku Ryoho; 8(5):735-742 1981

We investigated the pharmacokinetics of a newly developed water-soluble nitrosourea derivative, MCNU (1-(2-Chloroethyl)-3-(methyl-alpha-D-glucopyranose-6 yl)-1-nitrosourea) in three cases of malignant glioma and three cases of metastatic brain tumor following one-shot iv injection. A major portion of the MCNU was excreted in the urine. The pharmacokinetics was estimated by two-compartment open model analysis. The distribution rate was very fast, the half-life of alpha-phase being 4.4 min. The elimination rate was slow, the half-life of beta-phase being 41 min, and 65.4% of the MCNU moved into the tissue compartment. The MCNU level in the cerebrospinal fluid (ventricle) in two cases of metastatic brain tumor was measured. The max concentration of MCNU was 0.37 ug/ml 40 min after iv injection and corresponded to 30.5% of the level in the blood. the max MCNU level in malignant glioma tissue was 2.38 ug/g at 10 min and 3.31 ug/g in metastatic brain tumor tissue at 20 min. MCNU tended to move into glioma and metastatic brain tumor tissue. These results suggest that MCNU moves into brain tumor tissue and cerebrospinal fluid and that it may become a candidate drug for brain tumors. (26 Refs) (In JPN)

38. ENHANCEMENT OF ANTITUMOR EFFECT BY MAGNETIC CONTROL OF A MICROENCAPSULATED ANTICANCER DRUG.

Kato T
Dept. Urology, Akita Univ., Sch. Medicine, Hondo, Akita 010, Japan
Gan To Kagaku Ryoho; 8(5):698-706 1981

Responding to the need for selective cancer chemotherapy, magnetically controlled chemotherapy was investigated. For this purpose, two types of ferromagnetic mitomycin C microcapsules were prepared: an outer type with mean particle size of 308 um containing mitomycin C as a core covered with ethylcellulose and ferrite particles, and an interior type with mean particle size of 250 um containing both mitomycin C and ferrite particles as a core covered with ethylcellulose. In vitro analysis of these capsules indicated their sustained-release property and sensitive magnetization. Animal studies showed that the capsules could be guided in the aorta under the usual magnetic filed exerted from a conventional magnet. V2 tumors in the rabbit limb and urinary bladder were successfully treated by magnetic control of the capsules in the artery and bladder, respectively. Pharmacokinetic studies revealed that the magnetically controlled chemotherapy markedly increased the prolonged drug absorption into the target tissues, thus enhancing the antitumor effect of the encapsulated drug. The results strongly suggest the feasibility and effectiveness of magnetic control of a microencapsulated anticancer drug in the artery and/or luminal spaces. The prospect of this kind of cancer treatment is discussed. (11 Refs) (In JPN)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

39. NOVEL MAYTANSINOID TUMOR INHIBITORS FROM TREWIA NUDIFLORA: TREWIASINE, DEHYDROTREWIASINE, AND DEMETHYLTREWIASINE.

Powell RG, Weisleder D, Smith CR
Northern Regional Res. Center, Agricultural Res. Service, United States Dept. Agriculture, Peoria, IL, 61604
J Org Chem; 46(22):4398-4403 1981

Alcoholic extracts of Trewia nudiflora seed have yielded several new maytansinoid tumor inhibitors that are exceptionally active in the PS, B1, and KB systems. These include trewiasine, dehydrotrewiasine, and demethyltrewiasine, which were characterized by NMR, mass spectral and chemical correlation with other known maytansinoids. Two additional maytansinoids, trenudine and treflorine, have been partially characterized. The Trewia ansa macrolides differ from others in this series in that they possess an additional methoxy group at C-15; and, with the exception of trewiasine, they contain substituents at C-3 which differ from other known maytansinoids. Detailed 13C NMR assignments for maytansine and some related maytansinoids are presented. (Author abstract) (21 Refs)

40. AN IN VITRO MODEL FOR ACUTE MYELOGENOUS LEUKEMIA CHEMOTHERAPY.

Koeffler HP, Yen J, Lowe L
Dept. Medicine, Center Health Sciences, Univ. California, Los Angeles, CA, 90024
Cancer; 48(9):1958-1963 1981

A human acute myelogenous leukemia cell line that forms colonies in soft-gel culture (KG-1) was used to test the effect of various schedules and combinations of chemotherapeutic agents. For comparison, the drug sensitivity of normal human marrow myeloid clonogenic cells was tested. Cytosine arabinoside inhibited both the KG-1 and normal human colony-forming cells (CFC) approx 25% after a 2-hr exposure, 50% after a 5-hr exposure, and 90% after a 24-hr exposure. Daunorubicin had nearly an equal cytotoxic effect on KG-1 and normal marrow CFC after a 2-to 72-hr exposure to the drug. Daunorubicin at 0.15 ug/ml produced nearly complete inhibition of colony-forming cells. Amphotericin B also inhibited colony formation. Amphotericin B and daunorubicin, when combined in culture, produced a synergistic suppression of normal and leukemic CFC. The antileukemic agent 5-azacytidine at a concentration of 0.1 ug/ml produced approx 60% inhibition of colony formation. Cytidine partially rescued CFC when the nucleoside was added in seven-fold excess to cultures containing 5-azacytidine. Leukemic and normal marrow clonogenic cells have nearly the same sensitivity to each chemotherapeutic agent and combination. Human acute myelogenous leukemia lines may provide useful models for the development of new chemotherapeutic schedules and combinations. (Author abstract) (47 Refs)

41. PLANT ANTICANCER AGENTS. XI. 2,6-DIMETHOXYBENZOQUINONE AS A CYTOTOXIC CONSTITUENT OF TIBOUCHINA PULCHRA.

Jones E, Ekundayo O, Kingston DG
Dept. Chemistry, Virginia Polytechnic Inst., Blacksburg, VA, 24061
J Nat Prod; 44(4):493-494 1981

Separation by chromatography on silica gel of a methanol extract of ground material from woody stems of Tibouchina pulchra yielded a fraction with a 50% effective dose of 2.5 ug/ml in KB cell culture. Further purification by preparative thin-layer chromatography yielded a compound identified as 2,6-dimethoxybenzoquinone as the only identifiable cytotoxic material. (5 Refs)

42. EFFECT OF ALLITHIAMINE ON SARCOMA-180 TUMOR GROWTH IN MICE.

Cheng HH, Tung TC
Dept. Biochemistry, Taipei Medical Coll., Taipei, Taiwan
J Formosan Med Assoc; 80(4):385-393 1981

Garlic and its constituents, alliin and allicin, have been reported to have various pharmacological activities, including antitumor. The effects of garlic and its derivatives on growth of sarcoma-180 (S-180) are described. A mixed feed containing 4% powered garlic when fed daily to male NIH white mice inhibited growth of transplanted (sc on back) sarcoma-180 cells. When mice were inoculated sc with 2.5 x 10(5) S-180 cells followed by daily intratumoral injections (0.75 mg) of allicin extracted from garlic 24 hr later for 8 consecutive days, tumor growth was markedly inhibited (approx 70%). Alliin extracted from garlic showed no inhibitory effect on S-180 cells when tested in the same manner. Due to the instability and high cytotoxicity of allicin, its relatively stable and nontoxic derivatives, allithiamine and S-(thioallyl)-cysteine (produced by reaction with thiamine and cysteine respectively) were tested po and by intratumoral injection. Only intratumoral allithiamine exhibited marked inhibition of S-180. Garlic sugar and protein extracts injected intratumorally did not show antitumor activity. The possible mechanisms of the antitumor activities of allicin and allithiamine are discussed. (28 Refs) (In CHI)

43. PHARMACOLOGICAL STUDIES ON A PLANT LECTIN, ALOCTIN A. I. GROWTH INHIBITION OF MOUSE METHYLCHOLANTHRENE-INDUCED FIBROSARCOMA (METH A) IN ASCITES FORM BY ALOCTIN A.

Imanishi K, Ishiguro T, Saito H, Suzuki I
(c/o Suzuki) Lab. Ultrastructure Res., Aichi Cancer Center Res. Inst., Nagoya 464, Japan
Experientia; 37(11):1186-1187 1981

A glycoprotein isolated from Aloe arborescens Mill markedly inhibited the growth of a syngeneic transplantable fibrosarcoma of mice, Meth A, in ascites form. There is evidence that the inhibition mechanism is host-mediated and not a direct toxic effect on the tumor cell. (Author abstract) (13 Refs)

44. 6-GERANYLOXY-3-METHYL-1,8-DIHYDROXYANTHRONE, A NOVEL ANTILEUKEMIC AGENT FROM PSOROSPERMUM FEBRIFUGUM SPRACH VAR. FERRUGINEUM (HOOK. FIL).

Amonkar A, Chang CJ, Cassady JM
(c/o Cassady) Sch. Pharmacy and Pharmacal Sciences, Purdue Univ., West Lafayette , IN, 47907
Experientia; 37(11):1138-1139 1981

A systematic fractionation of the root extract of Psorospermum febrifugum was carried out in an attempt to reisolate the antitumor xanthone psorospermin and related compounds for further structural work and testing. This activity-directed fractionation led to the isolation of 6-geranyloxy-3-methyl-1,8-dihydroxyanthrone. This compound was characterized based on spectroscopic and chemical evidence and showed borderline but reproducible activity in the P-388 mouse leukemia system. (Author abstract) (10 Refs)

45. UREIDO-ETHYL-IMIDAZOLINES ACTIVE AGAINST AUTOCHTHONOUS DIETHYLNITROSAMINE-INDUCED EPIDERMOID, PAPILLARY AND ADENOCARCINOMATOUS TUMORS OF THE RESPIRATORY TRACT OF SYRIAN HAMSTERS AND AGAINST HUMAN BRONCHOGENIC CARCINOMAS IN NU/NU MICE.

Marxer A, Schmidt-Ruppin KH
Chemical and Biological Res. Lab., Pharmaceuticals Div. CIBA-GEIGY Ltd., CH-4002 Basel, Switzerland
Experientia; 37(11):1123-1131 1981

The detection of a new class of tumor inhibiting substances is described. Employing a chemical reaction discovered several yr ago, a series of imidazolinylureas were prepared. It was found that some compounds of this group were active against diethylnitrosamine (DENA)-induced tumors in hamsters. CGP 15720 A (1- *2-[2-(4-pyridyl)-2-imidazole-1-yl]-ethyl* -3-(4 carboxy-phenyl)urea), the most active compound at present, was developed through a series of structural variations. CGP 15720 A inhibits significantly in oral or parenteral treatment with well tolerated doses (10-30 mg/kg) the progressive growth of autochthonous, DENA-induced papillary, epidermoid and adenocarcinomatous tumors of the respiratory system in Syrian hamsters and prolongs significantly the survival. The substance also inhibits significantly the growth of two poorly differentiated human epidermoid or anaplastic bronchogenic carcinomas in nu/nu Balb/c mice and prolongs the mean survival time. In these mice, the substance is also active against the rodent ascites tumors Ehrlich carcinoma, CrSa 180 and Yoshida Sa AH 66, although it is only marginally active or inactive against these tumors in normal mice or rats. In the therapeutic trials, hamsters tolerated the highest dose administered for 4 wk, 1,000 mg/kg po, without signs or symptoms of toxicity (Author abstract) (35 Refs)

46. 2-L-RHAMNOPYRANOSYL[1,2,4]TRIAZOLO[1,5-A]PYRIDINE. 4' AND 3' OXIDATION PRODUCTS. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS.

Allard P, Dinh TH, Gouyette C, Igolen J, Chermann JC, Barre-Sinoussi F
Unite de Chimie Organique, Institut Pasteur, Equipe de Recherche Associee au CNRS (ERA 927), 75724 Paris, Cedex 15, France
J Med Chem; 24(11):1291-1297 1981

A series of 2-alpha-L-rhamnopyranosylnitro[1,2,4]triazolo[1,5 alpha]pyridine C-nucleosides was synthesized from the condensation of a thioiminoether with nitro-2-pyridylhydrazines. Catalytic reduction afforded the corresponding amino derivative. A 1',2' unsaturated C-nucleoside was also obtained by two different routes. Selective oxidation gave the 3'- and 4'-ketonucleosides. The cytotoxic properties of the nucleosides, as well as their effect on viral transformation and replication, were described. The nitro derivatives inhibit viral replication, but at toxic doses; the introduction of a keto function leads to a product which inhibits the replication of murine leukemia virus (MuLV) at noncytotoxic concentrations. The amino derivatives have no significant antiviral effect. (Author abstract) (26 Refs)

STUDIES OF ANTIMETASTATIC AGENTS

47. MANAGEMENT OF NON-SEMINOMATOUS TUMOURS (MEETING ABSTRACT).

Gittes RF, Richie JP, Garnick MB
Peter Bent Brigham Hospital and Sidney Farber Cancer Center, Boston, MA
Br J Urol; 53(1):68 1981

Radiation therapy has been abandoned in favor of combined surgery and chemotherapy in this disease. Cases without detectable metastases (Stage I) and those with early node involvement (elevated markers) but no bulky disease on computed axial tomographic (CAT) scan are treated with retroperitoneal node dissection, with care to protect the ejaculatory reflex by sparing the sympathetic ganglia and hypogastric plexus on one side. Only cases with detected distant metastases (Stage III) or 'bulky' nodes over 2 cm ('advanced' Stage II) detected by CAT scan, or positive markers after retoperitoneal node dissection receive chemotherapy in the form of 4 cycles of vinblastine (0.2 mg/kg/days 1,2), bleomycin (30 u weekly) and cis-platinum (20 mg/m(2)/days 1-5). They then have 'evaluative' surgical resection of residual retroperitoneal masses. Later they receive added cycles of adriamycin (50 mg/m(2)) and cyclophosphamide (500 mg/m(2)), 5 cycles if the excised tumor consisted only of mature teratoma or fibrosis and 10 cycles if 'active' or immature cells were found. About 90% of such advanced cases have been found free of disease at a median follow-up of 2 yr. Since retroperitoneal node dissection alone is a proven curative procedure for 80% of early Stage II cases, the later 'rescue' of the surgical failures by chemotherapy offers an overall better than 95% cure rate for Stages I to II, while sparing the vast majority from the rigors of chemotherapy and from the long-term limitations of radiotherapy. (no Refs)

INTERFERON AND OTHER ANTIVIRALS

48. DISPOSITION OF ANTIVIRAL DRUG ACYCLOVIR (ACV) IN HUMANS (MEETING ABSTRACT).

De Miranda P, Laskin O, Good S, Krasny hC, Connor J, Leitman P
Wellcome Research Laboratories, Research Triangle Park, NC
Program and Abstracts of the 21st Interscience Conference on Antimicrobial Agents and Chemotherapy, November 4-6, 1981, Chicago, Illinois American Society for Microbiology; 1981

The pharmacokinetic and metabolic disposition of (8-14C) ACV was investigated in 5 volunteers with advanced malignancies. The drug was administered by a 1-hr iv infusion at doses of 0.5 and 2.5 mg/kg. The plasma and blood radioactivity-time data and the plasma concentration-time data were defined by a two-compartment open pharmacokinetic model. There was nearly equivalent distribution of radioactivity in the blood and in plasma. The overall mean plasma terminal half-time and total body clearance +/- standard deviation of ACV were 2.1+/-0.5 hr and 297 +/-53 ml/min/1.73 m2. Binding of ACV to plasma proteins was 15.4 +/-4.4%. Most of the radioactive dose excreted was recovered in the urine (71 to 99%) with less than 2% excretion in the feces and only trace amounts in the expired CO2. High performance liquid chromatography analysis indicated that 9-carboxymethoxymethylguanine was the only significant urinary metabolite of ACV, accounting for 8.5 to 14.1% of the dose. A minor metablite (less than 0.2% of dose) had the retention time of 8-hydroxy-9-(2-hydroxyethoxymethyl)-guanine. Unchanged urinary ACV ranged from 62 to 91% of the dose. There was no indication of ACV cleavage to guanine. The renal clearances of ACV were approx 3-fold higher than the corresponding creatinine clearances. (no Refs)

49. SUPPRESSIVE EFFECTS OF INTERFERON ON CELL FUSION BY SENDAI VIRUS.

Tomita Y, Kuwata T
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
J Gen Virol; 55(part2):289-295 1981

Suppressive effects of human IFN-alpha, IFN-beta and mouse-IFN on syncytium formation in human and mouse transformed cells have been studied using UV-irradiated Sendai virus (UV-Sendai virus). After treatment of human RSa cells with 500 units/ml human IFN-alpha for 16 hr, the syncytium formation induced by UV-Sendai virus was reduced to less than 10% of controls. The suppressive effect was dependent on the amount of interferon added, and it was blocked by the addition of cycloheximide. Suppression of syncytium formation was also observed on human IFr cells, which are partially resistant to the anticellular effect of interferon but are sensitive to the antiviral effect of interferon. Human IFN-beta also had a suppressive effect on syncytium formation in human transformed cells, and human IFN-alpha, IFN-beta and mouse IFN showed species specificity in their effect on fusion. This anti-cell fusion activity was developed in IFr cells from about 5 hr after addition of IFN-alpha and when the cells were treated with IFN-alpha for 16 hr, the resistant state of cells continued for over 20 hr after removal of IFN-alpha. (Author abstract) (32 Refs)

50. COMPARATIVE STUDY OF ANTIVIRAL AND ANTIPROLIFERATIVE ACTIVITIES OF HUMAN INTERFERON ISOLATED FROM SUSPENSION AND STATIONARY CULTURES OF DONOR LEUKOCYTES.

Timofeev IV, Kuznetsov VP, Mekhedov LN, Nikolaeva TG, Orlova TG, Dobrynin IaV

N. F. Gamaleia Inst. Epidemiology and Microbiology, All-Union Cancer Res. Center, Moscow, USSR

Antibiotiki; 26(9):703-705 1981

Human interferons (IFs) isolated from the suspension cultures (IF-1) and stationary cultures (IF-2) of donor WBC showed comparable inhibitions of proliferative activity in CaOv cells. The antiviral activity of the IF-2 was lower than that of the IF-1. (8 Refs) (In RUS)

51. A NEW SCREENING PROCEDURE ON SELECTIVE INHIBITORS AGAINST SV40-TRANSFORMED CELLS.

Munekata M, Takatsuki A, Onodera K, Tamura G

Res. and Development Lab., Sapporo Breweries LTD.,, Mita, Meguro-ku, Tokyo 153, Japan

Agric Biol Chem; 45(8):1843-1854 1981

An in vitro assay method of cytotoxicity (N/T assay) and the basic data for N/T assay with several well-known antitumor agents are described. When six compounds were tested in parallel, WIRL-3 epithelial cells and their Simian virus 40 (SV40)-transformed counterparts were more sensitive than C3H-2K fibroblasts and SV40-transformed C3H-2K cells. Patterns of drug sensitivity were different between C3H-2K and SV40-C3H-2K cells. C3H-2K and SV40-C3H-2K cells were used for subsequent experiments. In the method adopted as the standard experimental procedure (namely N/T assay), cells were seeded at 1-2 x 10(4) per one well, and after 20-24 hr of incubation, the medium was replaced with a fresh drug-containing medium. After 72 hr of continuous exposure to the drug, the cells were washed with fresh medium, and refilled with a fresh medium without drugs. The inhibitory effect of well-known antitumor agents having different mechanisms of action are described. The results of testing 61 compounds with/without antitumor activity indicated that antitumor agents with the exception of antimetabolites do not have the selective cytotoxicity generally found in vitro. The pattern of selective cytotoxicity in vitro was classified into five groups by the N/T assay. The antimetabolites belonging to the Group I showed continuous and higher selective cytotoxicity. Bleomycin, oligomycin, and rifampicin, members of Group II had continuous and middle selective cytotoxicity. Group III consisting of energy transfer inhibitors and tunicamycin showed a specific pattern of cytotoxicity, ie, high selective cytotoxicity on day 1, none after day 2. Group IV, including actinomycin D, chromomycin, and cycloheximide, showed middle selective cytotoxicity on day 1, but none after day 2. Group V, including vinblastine, colchicine, mitomycin C, and many antitumor agents, had no selective cytotoxicity even at low concentrations. (20 Refs)

52. REDUCTION OF SIMIAN VIRUS 40 GROWTH BY A MITOTIC INHIBITOR EXTRACTED FROM LIVER. EVIDENCE THAT THE INHIBITOR IS ARGINASE.

Campadelli-Fiume G, Scannavini M, Falasca A, Hakim G, Busi C, Mattioli A, Fiume L

Istituto di Microbiologia e Virologia, Universita di Bologna, via San Giacomo 12, 40126 Bologna, Italy

Ann Sclavo; 23(2):162-168 1981

The effect of liver preparation was studied on the growth of SV 40 in CV1 cells, trying to establish whether the inhibitory effect was due to enzymatic destruction of one of the amino acids, present in the culture medium, and essential for cell DNA synthesis and growth. The mitotic inhibitor was extracted from rat liver and prepared as reported before. Max inhibition was obtained with 50 ug liver preparation protein/ml medium. When only the liver preparation and medium were incubated arginine disappeared and ornithine appeared, which suggest that liver preparations contain the enzyme arginase, which transforms arginine into ornithine. The addition of arginine to liver preparations completely prevented inhibition of cell growth. Liver preparations exhibit antiviral properties, which are probably due to lack of arginine. Most viruses (adeno, herpes, vaccina, reo, and papova) require arginine for their replication. (26 Refs)

OTHER RELATED STUDIES

53. RESISTANCE AGAINST CIS-DICHLORODIAMMINEPLATINUM IN CULTURED CELLS WITH A HIGH CONTENT OF METALLOTHIONEIN.

Bakka A, Endresen L, Johnsen AB, Edminson PD, Rugstad HE

Dept. Surgery, Akershus Central Hosp., N1474 Nordbyhagen, Norway

Toxicol Appl Pharmacol; 61(2):215-226 1981

Resistance against the antitumor drug cis-dichlorodiammineplatinum (cis-DDP) was investigated in cultured cells with a high metallothionein (MT) content. Human epithelial cells (HE), mouse fibroblast cells (C1 1D), and Cd-resistant substrains of both cell lines (HE100 and C1 1D100, respectively) were tested. Spectrophotometry and amino acid analysis confirmed that cytoplasmic Cd-binding proteins in Cd-resistant strains were MT. After cis-DDP treatment (3-60 uM), sensitivity was tested by colony formation in soft agar or monolayer for C1 1D and C1 1D100 cells. All cell types were tested by interval counting over a 4-day growth period (0.5-60 uM cis-DDP). Results after 15 uM cis-DDP for 1 hr showed a 3.7% survival for C1 1D cells and 31.4% for C1 1D100 cells. Results of cell counts were dose-dependent: at 5 uM cis-DDP, values were 12.7% of control growth for C1 1D, 51.1% for C1 1D100, 8.4% for HE, and 31.7% for HE100. The results suggest correlation between high content of low mol wt Cd-binding proteins and resistance against cis-DDP. Possible mechanisms for development of resistance include increased DNA repair, cell location in 'tumor sanctuaries,' and increased synthesis of glutathione which can sequester toxic chemicals. (53 Refs)

54. DRUG SENSITIVITY OF RAT BLADDER CANCER IN SYNGENEIC HOSTS AND ATHYMIC NUDE MICE.

Kitagawa H, Nakamura M, Kiuchi Y, Iwaguchi T
Div. Experimental Animals, Tokyo Metropolitan Inst. Medical Sci., Tokyo, Japan
Gan; 72(5):802-805 1981

The effects of chemotherapeutic agents on BC-47 rat bladder cancer were investigated in nude mice and syngeneic hosts to clarify the influence of host factors on chemotherapy. The BC-47 cancer was rich in stroma and lacked central necrosis in syngeneic ACI/N rats. In contrast, in nude mice it had little stroma and underwent necrosis in the center, and cancer cells proliferated primarily at the periphery in contact with the normal host tissue. The cancer showed similar patterns of sensitivity to bleomycin, 1,3-bis(2-chloroethyl)-1-nitrosourea, 5-fluorouracil, and mitomycin C in both hosts. In contrast, adriamycin and pyranyl secalonic acid D (pyranyl secalonic acid) had different effects in the two hosts, being significantly effective in rats, but ineffective in nude mice. (Author abstract) (6 Refs)

55. EFFECT OF BETA ADRENERGIC AGONISTS AND BETA BLOCKING AGENTS ON HEMOPOIESIS IN HUMAN BONE MARROW.

Dresch C, Minc J, Poirier O, Bouvet D
Service de Medecine nucleaire, 2, place du Docteur-Fournier, 75474 Paris Cedex 10, France
Biomedicine; 34(4):93-98 1981

The effect of propanolol (nonspecific blocking agent), acebutol (beta1 blocking agent), butoxamine (beta2 blocking agent) and several beta adrenergic agonists was studied on 3H-thymidine (3H-TdR) incorporation and granulomonocyte colony formation in agar by human bone marrow. Only butoxamine and propanolol decreased 3H-TdR incorporation by total normal bone marrow cells at concentrations above 10(-6) M for butoxamine and 10(-5) M for propanolol. Autoradiography showed that inhibition of 3H-TdR incorporation by butoxamine was slightly more pronounced on neutrophil precursors than on red cell precursors (neutrophil series LI..53 and erythroblasts .67 compared to control bone marrow cells at 10(-5) M concentration). The development of granulo-monocyte colonies in agar culture was delayed by preincubation with butoxamine at concentrations above 5 x 10(-6) M. Hydroxyurea suicide showed that this was due to a decrease in the number of CFU-C in S phase. Beta2 blocking agents are able to decrease the number of normal hematopoietic cells entering S phase. This effect is seen on both neutrophil and erythroblastic precursors and on granulo-monocyte progenitors. It could be used as a means of protecting bone marrow cells during cancer intensive chemotherapy. (Author abstract) (18 Refs)

56. ENHANCED ADRIAMYCIN-INDUCED DELAYED GASTROINTESTINAL RADIOSENSITIVITY IN TUMOR-BEARING MICE.

Kovacs CJ, Schenken LL, Evans MJ, Burholt DR
Dept. Radiology, Section Radiotherapy, Bowman Gray Sch. Medicine, 300 S. Hawthorne Road, Winston-Salem, NC, 27193
Int J Radiat Oncol Biol Phys; 7(10):1389-1395 1981

Drug-induced delayed gastrointestinal radiosensitivity, as measured by the proliferative compensatory kinetic response, was studied in BDF1 mice. Relative proliferative activity of the intestinal epithelium was determined by incorporation of 3H-thymidine into acid insoluble material. Intestinal proliferative activity in mice with implanted Lewis lung carcinoma

(LLcaBDF1) was markedly depressed with increasing tumor burden compared to that in non-tumor bearing (BDF1) mice. After a radiation dose of 600 rad, the presence of tumor (mean vol 859 +-209 cubic mm) delayed the jejunal response to radiation by 24 hr and reduced integrated cell production from 136% in BDF1 mice to 119% in LLca/BDF1 mice. While presence of tumor did not alter the temporal response of colonic epithelium to radiation, the compensatory peak was reduced from 248% (BDF1) to 200% (LLca/BDF1). Adriamycin (ADR; 10 mg/kg) given 60 days prior to radiation failed to enhance jejunal radiosensitivity in BDF1 mice. Similar ADR treatment of mice with LLca tumor delayed the peak of compensatory hyperplasia from 48 hr to 72 hr; there also was a slight increase in magnitude of the peak. (18 Refs)

57. DIFFERENTIAL INDUCIBILITY OF CHROMOSOME ABERRATIONS AND SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS IN VARIOUS MAMMALIAN CELL LINES.

Ikeuchi T, Sasaki M
(c/o Sasaki) Chromosome Res. Unit, Hokkaido Univ., Sapporo 060, Japan
Mutat Res; 90(2):149-161 1981

A variety of mammalian cell cultures were examined for inducibility of chromosomal aberrations (CA) and sister chromatid exchanges (SCE) by the indirect mutagens cyclophosphamide (CP), dimethylnitrosamine (DMN), and benzo(a)pyrene (BP). Sixteen cell lines were examined for response to CP. All rat ascites hepatoma cell lines showed a significant increase in frequencies of both SCE and CA in a dose-dependent manner. Several rat esophageal tumor cell lines showed an extremely high sensitivity to CP, with significant yields of SCE and CA obtained at much lower concentrations compared to other cell lines. Seven cell lines were examined for their responsiveness to DMN. AH66-B, R1 and R3 cells, which showed a significant response to CP, were also sensitive to DMN in induction of CA. SCE frequency increased only slightly, however. Of the four cell lines studied for BP sensitivity, GHE cells showed the highest response to BP; frequencies of both SCE and CA were increased up to 3.8-and 6.9x. AH66-B and B-13 were moderately sensitive. HE2144 was almost insensitive but showed slightly increased frequency of SCE. (28 Refs)

58. POSSIBLE REQUIREMENT OF INTERNALIZATION IN THE MECHANISM OF IN VITRO CYTOTOXICITY IN TUMOR NECROSIS SERUM.

Kull FC, Cuatrecasas P
Dept. Molecular Biology, Wellcome Res. Lab., Res. Triangle Park, NC, 27709
Cancer Res; 41(12):4885-4890 1981

The mechanism of in vitro cytotoxicity by tumor necrosis serum (TNS) and a purified fraction was examined using sensitive L-M cells. Cell death was assessed by uptake of the dye trypan blue and/or by release of radiolabeled chromium. Cell killing was time and dose dependent. Cell survival was assessed by counting the number of survivors via their ability to internalize the dye neutral red and/or by adherent cell protein. The cytotoxin was not cytostatic. Survival was found to be inversely proportional to cell death. The change in survival was used to estimate the number of cells killed. The number of cells killed was logarithmically related to the amount of toxin. The ability to kill a fixed number of cells was inversely related to the number of cells in the assay well. It was estimated that, at ideal cell seed numbers, 1 ug of TNS protein per 250 ul killed about 50,000 cells in a 20-hr period. Sensitivity was equated with the amount of TNS required to kill 35,000 cells in 20 hr. Inhibitors of RNA and protein synthesis and also elevated temperatures enhanced sensitivity. The combined treatment of 1 uM actinomycin D and 40 C enhanced sensitivity by 15-fold. Resistant normal and tumorigenic cell lines (including human) were rendered sensitive by concomitantly treating them with TNS and cycloheximide or actinomycin D. Cytoskeletal-disrupting agents (colchicine, Colcemid and cytochalasin B), inhibitors of lysosome activity (chloroquine, methylamine, and leupeptin), and 32 C all depressed sensitivity. Sensitivity was nearly equivalent in calcium-free medium. Results substituting partially purified cytotoxin were similar. The results suggest that a toxic factor(s) may need to be internalized and that lysosomal activity may be necessary for cell killing. Comparisons with lymphotoxin are discussed. (Author abstract) (41 Refs)

59. EFFECT OF VINBLASTINE ON DISTRIBUTION OF MURINE LEUKEMIA VIRUS-DERIVED MEMBRANE-ASSOCIATED ANTIGENS.

Satake M, McMillan PN, Luftig RB
Dept. Microbiology and Immunology, Univ. South Carolina Sch. Medicine, Columbia, SC, 29208
Proc Natl Acad Sci USA; 78(10):6266-6270 1981

The effect of vinblastine on the distribution of murine leukemia virus-derived membrane-associated antigens was examined by using the indirect immunofluorescence of 3.7% formaldehyde-fixed MJD-54 (Moloney murine leukemia virus-infected) cells. On fixed, non-drug-treated cells, p30 antigen was distributed homogeneously and diffusely over the cell membrane. When cells were incubated with 10 uM vinblastine for 1 hr before fixation, the distribution of p30 antigen was greatly changed, fluorescence now being collected into poles (cap-like formation). In contrast to this distribution pattern for p30 antigen, gp70 antigen was distributed in a micropunctate pattern on the cell surface, with or without vinblastine pretreatment. These observations indicate that the distribution patterns of p30 and gp70 membrane antigens are completely different and that they are differently controlled by cytoplasmic microtubules. In addition, because the p30 membrane antigen visualized in these studies most likely represents viral Pr65gag precursor molecules which are localized directly under and associated with the plasma membrane, these results suggest that, under special conditions of fixation, it is possible to obtain a cap-like phenomenon for cytoplasmic (internal) membrane-oriented proteins. (Author abstract) (24 Refs)

60. ANTAGONISM OF DRUGS USED IN LEUKAEMIA THERAPY TO THE KILLING OF HUMAN LYMPHOBLASTOID CELLS BY STEROID.

Gledhill RM, Norman MR
Dept. Chemical Pathology, King's Coll. Hosp. Medical Sch., Denmark Hill, London SE5 8RX, England
Br J Cancer; 44(3):467-471 1981

The interactions of prednisolone with drugs currently used in the chemotherapy of acute lymphoblastic leukemia were studied in human lymphoblastoid cell line CCRF-CEM-7, the cells of which are lysed by pharmacological concentrations of glucocorticoids. Determination of cell survival in the presence of prednisolone alone and in combination with 6-mercaptopurine (MP), methotrexate (MTX), cytosine arabinoside (Ara-C), and daunomycin (DMN) showed no consistent interaction between MTX and prednisolone. Interactions between DMN and prednisolone varied between mild synergism and antagonism, while both MP and Ara-C showed consistent antagonism. (14 Refs)

61. THE PHARMACOLOGY OF THE FLUOROPYRIMIDINES.

Myers CE
Biochemical Pharmacology Section, Clinical Pharmacology Branch, Clinical Oncology Program, Div. Cancer Treatment, NCI, Bethesda, MD
Pharmacol Rev; 33(1):1-15 1981

The pharmacology of the antitumor agent 5-fluorouracil (FUra) and its metabolites is reviewed. FUra can be activated by thymidine phosphorylase to fluorodeoxyuridylate. A series of conversions leads to the incorporation of 5-fluorodeoxyuridine triphosphate into DNA; resultant effects include misreading of DNA. A metabolite of FUra, 5-fluorodeoxyuridine monophosphate, interacts with thymidylate synthetase (TS). Chemistry and kinetics of this interaction are discussed. The relative importance of RNA effects and TS inhibition is considered. Sequential inhibition of de novo synthesis of thymidylate is discussed as a factor in chemotherapy. Selective antifungal effects of fluorocytosine are described. Pharmacokinetics of FUra are presented, including methodological considerations, means of administration, pharmacokinetics of oral FUra, and pharmacology of intraperitoneal FUra. (125 Refs)

62. CHRONIC MYELOID LEUKEMIA (A STATE OF THE ART REPORT).

Chrobak L
I. Vnitrni klinika fakulty, Universita Karlova, 500 36 Hradec Kralove, Czechoslovakia
Vnitr Lek; 27(9):899-904 1981

Chronic myeloid leukemia (CML) is a clonal disease due to an affection of the pluripotent Philadelphia chromosome-positive and -negative stem cells. The clonal origin of CML is demonstrated by the study of the glucose-6-phosphate dehydrogenase isoenzymes. The significance of the Philadelphia chromosome in the origin of the pathological clone is still unclear, and it cannot be ruled out that it represents a secondary phenomenon. The disease develops in two phases: the chronic phase, usually with a favorable response to treatment, and an accelerated phase, ending in blastic conversion in the majority of the cases, which conversion is heralded sometimes by changes in the behavior of granulocyte colonies in vitro. Besides myeloblastic conversion, lymphoblastic conversion with a favorable response to vincristine and prednisone occurs in almost 30% of all cases. The increasing incidence of meningeal affections is due to the increasing remission rate. Busulfan continues to be used in the treatment during the chronic phase of CML. Splenectomy during the early phase of the disease proved to be ineffective. (69 Refs) (In CZE)

63. TAMOXIFEN-INDUCED GENERALIZED LIPIDOSIS IN RATS SUBCHRONICALLY TREATED WITH HIGH DOSES.

Lullmann H, Lullmann-Rauch R
Dept. Pharmacology, Univ. Kiel, Kiel, W. Germany
Toxicol Appl Pharmacol; 61(1):138-146 1981

To determine whether the antiestrogenic and antineoplastic agent tamoxifen (TMX) induces generalized lipidosis, female Wistar rats were kept on a TMX-containing diet for 6-14 wk. The daily TMX doses ranged 100 to 130 mg/kg. Light and electron microscopic examination of liver, popliteal lymph nodes, adrenal glands, anterior pituitary gland, retina, nucleus supraopticus of the hypothalamus, and superior cervical ganglion showed increased numbers of intensely staining lamellated and crystalline-like cytoplasmic inclusions. Necrosis and gradual replacement by abnormal vacuolated cells were observed in the adrenal cortex. The degree of lipidosis depended upon the dose of TMX and duration of treatment. (15 Refs)

64. INTERACTION OF VP 16-213 WITH DNA REPAIR ANTAGONISTS (MEETING ABSTRACT).

Arnold AM, Whitehouse JM
CRC Medical Oncology Unit, Southampton, England
Br J Cancer; 43(5):733 1981

The podophyllotoxin derivative VP 16-213 can apparently cause single-stranded breaks in DNA, capable of repair. Several compounds are known to be powerful inhibitors of DNA repair, so it was of interest to study the interactions of VP 16-213 with chloroquine and caffeine. Female DBA mice weighing 20 g were inoculated sc with 10(5) TLX lymphoma cells. Three days after inoculation the animals were treated with VP 16-213, together with either chloroquine (20-40 mg/kg) by ip injection or caffeine (0.125-1%) added to the drinking water. By way of a control, vincristine, a drug not thought to damage DNA, was also tested with chloroquine. Results were expressed as increased lifespan (ILS) over untreated controls. VP 16-213 alone (6.25 mg/kg and 12.5 mg/kg) produced an ILS of 9% and 30% respectively. VP 16-213 in the same doses but together with 40 mg/kg chloroquine produced ILS of 78% and 76% respectively. By contrast chloroquine did not enhance the effect of vincristine. One per cent caffeine added to drinking water of animals given VP 16-213 produced a significant but less marked ILS. These preliminary observations provide further evidence that the mode of action of VP 16-213 may be due to the formation of single-stranded breaks in DNA, though it is possible that other mechanisms may be responsible for the apparent synergism. (no Refs)

65. MODE OF ACTION STUDIES OF THE ANTITUMOR ANTIBIOTIC TOROMYCIN AND THE RELATED COMPOUND CHRYSOMYCIN (MEETING ABSTRACT).

Wei TT, Byrne K, Elespuru R, Greenstein M, Pickle D, Richardson C, Stroshane R, Weiss U, White RJ
Frederick Cancer Research Center, Frederick, MD
Program and Abstracts of the 21st Interscience Conference on Antimicrobial Agents and Chemotherapy, November 4-6, 1981, Chicago, Illinois American Society for Microbiology; 1981

The mechanism of action of toromycin, a new antitumor antibiotic, and the closely related compound chrysomycin was investigated. Macromolecular synthesis studies in Bacillus subtilis indicated that upon addition of toromycin or chrysomycin, nucleic acid synthesis was inhibited preferentially to protein synthesis. In particular, inhibition of DNA synthesis was more complete than RNA synthesis. Both toromycin and chrysomycin demonstrated strong activity in the biochemical prophage induction assay (BIA), a sensitive test for agents interacting with DNA. Interaction of these compounds with DNA in vitro was detected by an acridine orange competitive fluorescence polarization assay. Agarose gel electrophoresis of supercoiled DNA indicated that toromycin binds by intercalation at concentrations less than 5 ug/m/. Our data suggest that drug interaction with DNA plays a prominent role in the biological activity of this new type of antitumor antibiotic. (no Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

ANTITUMOR AGENT EFFICACY IN VIVO

1. THERAPEUTIC EFFICIENCY OF ADRIAMYCIN IN MICE BEARING TRANSPLANTED OR AUTOCHTHONOUS SOLID TUMORS. DRUG AND FLUORESCENT METABOLITES PLASMAT LEVELS.

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Bull Cancer (Paris); 68(4):313-320 1981

The adriamycin (ADM) efficiency was studied in mice coming from various lines. These mice were either bearing solid, autochthonous tumors with differentiated histology induced by dimethylbenzanthracene (DMBA), or transplanted tumors. The variations of the parameters that characterize the tumoral growth were analyzed after some ADM injections. On one hand, the therapeutic efficiency (which was appreciated by tumoral volume percentage reduction), and on the other the tumoral growth delay, are positively correlated with the number of injections. After three ADM injections, 100% of transplanted tumors are showing a volumic reduction rate of 96% but as for the autochthonous tumors, 80% of the epithelial tumors are showing a reduction rate of 73% and, 8% of connective tumors only 24%. After treatment, a volumic reduction phase, is followed by a growth phase, the doubling time of which equals the preceding treatment one. For transplanted tumor and connective tumor bearing mice, survival delays are positively correlated with the number of injections. This correlation was not observed on epithelial tumor bearing mice. The plasmat levels of ADM and of its principal fluorescent metabolites (adriamycinol and adriamycinone) were obtained by a technique which presents both liquid chromatography efficiency and fluorescence sensitivity. ADM plasmat levels significantly increase with the number of injections. Those plasmat levels are correlated with the therapeutic efficiency on autochthonous sarcoma bearing mice. No correlation could be observed between metabolite levels and therapeutic efficiency. The interest respectively presented by each of those three experimental models is analyzed according to those results. (Author abstract) (16 Refs) (In FRE)

2. CHEMOTHERAPY OF AUTOCHTHONOUS MYELOID LEUKEMIAS (CHLOROLEUKEMIAS) IN WISTAR RATS.

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J Cancer Res Clin Oncol; 101(3):243-248 1981

Busulfan (BS) and cyclophosphamide (CPA) were used to treat chloroleukemia induced in male Wistar rats by the weekly iv injection of ethylnitrosourea (15 mg/kg). Eight leukemias were treated with BS (Group I), 14 with CPA (Groups II and III). BS in 0.1% suspension in water was applied daily, 5 days/wk po; the median total dose was 13.25 mg/kg. CPA was given ip in 2% soln in physiologic saline. Eight rats were given 20 mg/kg CPA weekly (Group II: median total dose 150 mg/kg), and six rats were given 50 mg/kg CPA weekly (Group III: median total dose 200 mg/kg). BS treatment produced only one temporary regression of hepatosplenomegaly; the remaining seven rats showed no response. The WBC count remained unchanged in all BS-treated rats; the median survival of these rats was 29.5 days, significantly shorter than untreated controls. Groups II and III showed median survival times of 69.5 and 61.5 days, respectively. Four of the eight Gro up II rats achieved a short (less than 8 days) remission, while the other four showed only a decrease in the peripheral cell number but no essential regression of the hepatosplenomegaly. All six Group III rats achieved complete remission with a median duration of 20 days (range: 8-50). The survival times for CPA-treated did not differ significantly from untreated controls. The comparability of autochthonous chloroleukemias in the rat with human chronic myeloid leukemia is discussed. (20 Refs)

3. RELATIONSHIP BETWEEN IN VIVO MITOMYCIN C EXPOSURE, SISTER CHROMATID EXCHANGE INDUCTION AND IN VITRO MITOGENIC PROLIFERATION. I. DEVELOPMENT OF MURINE SPLENIC CELL SYSTEM.

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Mech Ageing Dev; 17(2):195-201 1981

In vivo administration of mitomycin C (MMC) to C57BL/6J mice induced a rapid, initial suppression (24 hr post injection) of in vitro mitogenesis. This was followed by inhibition of phytohemagglutinin and concanavalin A mitogen responses that were no longer mitogen concentration independent (48-72 hr post injection). This can be seen in the mitogen concentration-response curves for the three mitogens, phytohemagglutinin, concanavalin A and lipopolysaccharide. By 144 hr post injection, the dose-response curves and magnitude of the responses had returned to approx control (untreated) levels. This approach provides a model system for the functional assessment of in vivo cellular damage by MMC. (Author abstract) (11 Refs)

4. INHIBITION OF 3H-TDR-INCORPORATION IN TUMOR CELLS AFTER APPLICATION OF CYTOTOXIC DRUGS AS AN INDICATOR OF THERAPEUTIC EFFECTIVENESS.

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Blut; 43(2):105-107 1981

THe prognostic value of the reduction of [3H]-thymidine (TdR) incorporation by tumor cells was studied in female Wistar rats. Tumors were produced in 36 rats by ip injection of 2 x 10(6) Walker ascites carcinosarcoma cells. Equal numbers of rats received 1 mg cis-platinum (DDP)/kg, 0.8 mg adriamycin (ADM)/kg, or 0.2 mg physiological saline ip. Ascites cell samples were obtained before injection, and at 3, 6, and 24 hr after injection. Therapeutic effectiveness of treatment was measured by survival time. The saline (control) group showed an increase in TdR incorporation from 2,681 +-270 cpm before injection (BI) to 3,062 +-203 cpm after injection (AI). The ADM group showed a decrease from 2,036 +-200 cpm BI to 1,639 +-225 cpm AI. The DDP group showed no significant change. Survival times were 4.7 +-0.3 days for controls, 6.0 +-0.5 days for the DDP group, and 9.0 +-1.2 days for the ADM group. Survival time corr elated well with change in TdR incorporation. (3 Refs) (In GER)

ANTITUMOR AGENT EFFICACY IN VITRO

5. BIOLOGICAL CHARACTERIZATION OF CELLS DERIVED FROM A HUMAN BREAST CARCINOMA: I. SOME CHARACTERISTICS OF CELLS CULTIVATED IN VITRO PRIOR TO AND AFTER TRANSPLANTATION INTO NUDE MICE.

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Arch Geschwulstforsch; 52(1):17-27 1982

Cells derived by collagenase treatment from a human breast carcinoma were characterized: cells from a tissue sample were grown in culture and then transplanted as ascitic or solid transplants into nude mice. Original tumor cells were primarily undifferentiated. Cells from the fifth in vitro passage were compared with ascitic and solid tumor cells. Ascitic cells showed the greatest proliferation and the highest frequency of polyploid cells. Cultured, ascitic, and solid-tumor cells had similar ultrastructure. Solid-tumor cells contained virus particles, while other cells did not. Original tumor cells (BO-0) showed significant binding of estrogen; all other cells lacked estrogen receptors. BO-0 cells were sensitive to vinblastine (VLB), 5-fluorouracil, daunoblastin, and sarkolysin. Cells from the first ascitic passage exhibited decreased sensitivity to VLB. Ascitic cells showed drug responses after several in vitro passages closer to those of BO-0 cells. Solid tumor cells showed different sensitivities to drug treatment from those of BO-0 cells. Results indicate that environmental dependencies must be taken into account when using in vitro and in vivo tumor models in cancer research. (28 Refs)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

6. INCREASED SCHEDULE-DEPENDENT SYNERGISM OF VINDESINE VERSUS VINCRISTINE IN COMBINATION WITH METHOTREXATE AGAINST L1210 LEUKEMIA.

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Cancer Treat Rep; 65(11/12):1049-1053 1981

BD2F1 mice were inoculated ip with 10(6) L1210 leukemia cells and treated with vincristine or vindesine alone or in combination with methotrexate. Drug administration was begun on Day 1 and was continued every 4 days until a total of five doses were given or death occurred. Methotrexate produced a 199% and a 222% increase in lifespan, respectively, as compared with untreated animals. When given as single agents, vincristine or vindesine produced between a 27% and an 88% increase in lifespan. The therapeutic benefit observed when either vinca alkaloid was used with methotrexate was schedule-dependent. When vindesine was administered with 72 mg/kg of methotrexate, the increase in lifespan was greater than expected from an additive effect of the two agents. However, none of the trials employing single-agent therapy or simultaneous combination therapy produced long-term survivors. When either vinca alkaloid was given 24 hr after the folate analog, the increase in lifespan was almost 100% greater than that observed when the agents were given simultaneously; moreover, long-term survivors were produced. Vindesine in combination with 48 mg/kg of methotrexate produced 10%-25% long-term survivors, as compared to 5%-7% long-term survivors obtained with vincristine. In combination with 72 mg/kg of methotrexate, vindesine produced 27%-60% long-term survivors, as compared to 10%-20% long-term survivors obtained with vincristine. When either vinca alkaloid was administered 72 hr after methotrexate, the regimen was still synergistic, but the overall effect was less than with a 24-hr delay. When two doses of either vinca alkaloid were injected at 24 and at 72 hr after the folate analog, the result was either highly therapeutic or very toxic. Two doses of 0.5 mg/kg of vindesine or vincristine with 48 mg/kg of methotrexate produced 35% and 20% long-term survivors, respectively. All other regimens were toxic. (Author abstract) (18 Refs)

7. EFFECTS OF NANDROLONE DECANOATE ON THE TOXICITY AND ANTI-TUMOUR ACTION OF CCNU AND FU IN MURINE TUMOURS.

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Br J Cancer; 44(4):572-577 1981

Pre-treatment with the anabolic steroid nandrolone decanoate (ND) increases the LD50 of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and 5-fluorouracil (FU) in NMRI mice. Administration of ND did not affect the anti-tumor action of CCNU against a transplantable mouse adenocarcinoma of the colon (MAC 13) or the anti-tumor action of FU against MAC 26. In both tumor lines ND had no significant effect on tumor growth. These data suggest that an increase in the anti-tumor selectivity of these agents may be produced by pretreatment with ND. (Author abstract) (17 Refs)

8. TRIPLE DRUG CHEMOTHERAPY IN TREATMENT OF PROSTATE ADENOCARCINOMA NB PR A.I.-III.

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Invest Urol; 19(3):191-193 1981

The combination of cyclophosphamide, cis-platinum, and adriamycin has been evaluated in the Nb tumor model system. Triple drug therapy has resulted in marked reduction in tumor volume (p less than 0.01), as well as decreased number of metastases (p less than 0.01). Combination chemotherapy has reduced the metastatic rate, increased complete tumor regression, and reduced the final tumor volume. The androgen insensitive tumor of Nb Pr AI-II was evaluated with combinations of BCNU and adriamycin in three cycles. The final tumor volume when compared to controls was significant for all of the agents evaluated (p less than 0.01). A significant decrease in the number of metastases was observed in the triple drug therapy, administered for three cycles, BCNU only, and BCNU and adriamycin. The acid phosphatase content of the treatment group's tumors, when compared to controls was significant with BCNU treatment only. (Author abstract) (13 Refs)

9. EFFECT OF THYMIDINE ON THE TOXICITY AND ANTITUMOR ACTIVITY OF FTORAFUR.

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Cancer Treat Rep; 65(11/12):1087-1091 1981

The effects of thymidine (TdR) on the toxicity and antitumor activity of ftorafur (FT), a 5-FU analog, were determined. The LD10 of FT was 130, 430, and 680 mg/kg, respectively, when FT was administered ip in the following treatment schedules: (a) daily for 9 days, (b) every 4th day for three treatments, and (c) 1 day only. When FT was administered simultaneously with 250 mg/kg of TdR, the LD10 was 13, 62, and 630 mg/kg in the respective treatment schedules. Lethargy was observed in mice when the daily dose of FT was greater than or equal to 150 mg/kg. FT alone was active (% treated/control [T/C] = 153) against ascites P388 murine leukemia only at high, single doses. Simultaneous administration of Ft and 250 mg/kg of TdR at or below the LD10 dose of FT resulted in an increase in the antitumor activity to a percent T/C of 217 (daily, Days 1-9) and 188 (daily, Days 1, 5, and 9). The activity of FT administered simultaneously with TdR on Day 1 only (% T/C = 142) was lower than that for FT alone. Using a treatment schedule of Days 1, 5, and 9, a TdR/FT mol ratio of greater than or equal to 2.0 seems necessary to achieve an increase in therapeutic value against P388 murine leukemia. This may explain the lack of increase in activity against P388 when 250 mg/kg of TdR was coadministered with FT on Day 1 only. FT alone or coadministered with 250 mg/kg of TdR was equally active against L1210 ascites tumor at doses up to the LD10 with daily treatments on Days 1, 5, and 9 and on Days 1-9; the doses of FT, however, were below those which cause lethargy. (Author abstract) (12 Refs)

10. EFFECT OF CONCURRENT CALCIUM LEUCOVORIN INFUSION ON 5-FLUOROURACIL CYTOTOXICITY AGAINST MURINE L1210 LEUKEMIA.

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Cancer Chemother Pharmacol; 6(2):121-125 1981

The ability of concurrent infusion of leucovorin (LV) to enhance efficacy of 5-fluorouracil (FUra) against mouse L1210 leukemia was studied. Treatment of B6D2F1 mice bearing the L1210 sc tumor with FUra (100 mg/kg) plus concurrent infusion with either LV (11.5 mg/kg/day) or 0.9% NaCl resulted in a 28% increase in median lifespan (ILS). Similarly, FUra (100 mg/kg) plus LV (115 mg/kg/day) or FUra (200 mg/kg) plus LV (115 mg/kg/day) also resulted in an ILS no different from that obtained with FUra (100 or 200 mg/kg) plus 0.9% NaCl infusion. A similar LV effect was noted when mice bearing L1210 ip tumors were treated with FUra and LV. LV infusion did not appear to increase the lethal toxicity of FUra; in each experiment, tumor-bearing mice treated with either FUra + LV or FUra + 0.9% NaCl died over approx the same range of days. No increase in toxicity was noted when nontumor bearing mice were given a single ip dose of FUra (200 mg/kg) and concurrent infusion with LV (115 mg/kg/day). The data indicated that concurrent LV infusion does not enhance FUra action against the mouse L1210 leukemia. (22 Refs)

11. EVALUATION OF NEW ANTHRACYCLINE ANALOGS WITH THE HUMAN TUMOR STEM CELL ASSAY.

Salmon SE, Liu RM, Casazza AM

Cancer Center, Univ. Arizona Health Sciences Center, Tuscon, AZ, 85724

Cancer Chemother Pharmacol; 6(2):103-109 1981

The human tumor stem cell assay (HTSCA) was used in a screening mode for simultaneous testing of 10 anthracyclines (AT: doxorubicin (DX), daunorubicin (DNR), and analogues), bearing various modifications in chemical structure and stereochemistry of the aglycone or aminosugar, against seven different human adenocarcinomas. At 10 ug/ml AT, the survival of tumor colony forming units (TCFU) from two breast, two ovarian, two endometrial and one gastric cancer was reduced to less than 1% of control in all cases, with the exception of one of the endometrial cancers. A spread of survival of TCFU over a two-log range was achieved for seven adenocarcinomas tested at AT dosage of 0.01 or 0.05 ug/ml. The greatest degree of inhibition of TCFU was observed with the two breast cancer specimens. Of the analogs, 4-deoxy-doxorubicin had the greatest in vitro potency (21% survival), followed in decreasing order by 4'-O-methyl-doxorubicin (26%), 4-demethoxy-4'-epi-doxorubicin (29%), 4-demethoxy-daunorubicin (31%), DNR (34%), 4-demethoxy-doxorubicin (36%), DX (46%), 4'-epi-doxorubicin (47%), 3'4'-diepi-doxorubicin (58%), and 11-deoxydoxorubicin (61%). Assessment of effects on tumor colony survival for the human tumors tested revealed that the three compounds lacking the methoxyl group in position 4 of the aglycone (4-demethoxyDX, 4-demethoxy-4'-epiDX, and 4-demethoxyDNR) were all more cytotoxic to TCFU than their parent compounds. Compounds modified in position 4'- of the aminosugar (ie, 4'epiDX) were either as toxic or more toxic (4'-deoxyDX and 4'-O-methylDX) than the parent compound DX. On av, 11-deoxyDX was less toxic than the parent compound DX or the other eight AT. (22 Refs)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

12. REVERSAL OF METHOTREXATE TOXICITY IN MICE BY A CALCIUM SALT OF CITROVORUM FACTOR AND RELATED COMPOUNDS.

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Cancer Treat Rep; 65(11/12):1117-1119 1981

The isolation of citrovorum factor from a chemically prepared mixture of the (+-) diastereoisomers (leucovorin) is described. The natural diastereoisomer was at least twice as effective as leucovorin in reversing methotrexate toxicity in mice. (Author abstract) (10 Refs)

13. ACUTE NEGATIVE INOTROPIC EFFECT OF ADRIAMYCIN (DOXORUBICIN).

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Naunyn Schmiedebergs Arch Pharmacol; 317(3):252-256 1981

Muscle mechanical effects of adriamycin (AD) were studied in isolated cardiac papillary muscles of male and female guinea pigs and Sprague-Dawley rats, while hemodynamic effects were studied in open-chest preparations of rats. Concentration-dependent decreases in max tension development of papillary muscle were produced by AD (10(-6) to 10(-3) M) which were 80% and 25% of control values in 21 guinea pigs and 15 rats, respectively. This negative inotropic effect was reversible after washout of low concentrations of AD (up to 3.5 x 10(-5) M), but not after higher concentrations. An antagonistic interaction was demonstrated between the cardio-depressant effect of AD and the positive inotropic effect of added Ca++ and vice versa. In in situ rat preparations, left ventricular pressure (LVP), max LVP rise, aortic pressure and cardiac output decreased in a dose-dependent manner after AD (2-30 mg/kg, iv) until lethal hemodynamic shock occurred. Serum Ca++ fell from control levels of 2.1 to 0.5 mEq after 25 mg/kg of AD. It is concluded that the acute muscle mechanical and hemodynamic effects of AD result from an interaction of AD and calcium. (40 Refs)

14. EFFECT OF HYDROXYUREA ON TWO DIFFERENT TYPES OF HEMATOPOIETIC STEM CELLS (CFU-S AND DCPC) OF NEWBORN MICE.

Ben-Ishay Z, Prindull G, Ben-Israel D
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Blut; 42(3):165-172 1981

The effect of hydroxyurea (HU: 1,000 mg/kg) on pluripotent hematopoietic stem cells from bone marrow was studied in newborn (9-13 days old) Sabra strain mice. Group I (75 mice) received a single ip injection of HU. Group II (30 mice) received two ip injections of HU 8 and 2 hr before killing. Group III (100 mice) received 2 ip injections/wk at 6-hr intervals for 4 wk (total of eight injections). Group I showed total bone marrow cellularity reduced to 30% of control levels after 24 hr, with normal composition restored within 7 days. Colony-forming units-spleen (CFU-S) were reduced to 15-40% of normal levels during the recovery period, while diffusion chamber progenitor cells (DCPC) increased to more than twice normal levels. In group II DCPC were twice normal levels 2 hr after the second HU injection. Group III had 60% mortality, and survivors were hypotrophic, underweight, and nude. CFU-S were markedly decreased. DCPC were 1-2 times normal levels. Results suggest that DCPC cells are less differentiated than CFU-S cells, and that under hemopoietic stress they proceed rapidly through the CFU-S stage to myelopoiesis. DCPC levels are suggested as a more accurate assay of hemopoietic regenerative capacity than CFU-S levels, at least in newborn mice. (16 Refs)

15. DIURNAL VARIATION IN THE INTESTINAL TOXICITY OF 5-FLUOROURACIL IN THE RAT.

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Clin Sci; 61(6):717-722 1981

The effect of time of administration of 5-fluorouracil (5-FU) on intestinal toxicity in the rat was studied. Male Wistar rats weighing 150-200 g received 187 mg/kg body wt ip at specified times during the day and night. Water absorption was measured in vitro. Variations in intestinal DNA content during the diurnal cycle were measured. Highest water absorption rates followed injection of 5-FU at 0200 hr. Diarrhea was minimized by injection of 5-FU between 0200 and 0300 hr. At other times 5-FU produced a high incidence of diarrhea. In the seven days following injection of 5-FU, water absorption was consistently higher in rats injected at 0200 hr (Group 1) than in rats injected at 1500 hr (Group 2). Rates returned to normal in both groups after 6 or 7 days. Body wt reached a minimum of 88% of preinjection wt (PIW) on day 4 in Group 1. A minimum of 82% of PIW was reached on day 5 in Group 2. Intestinal DNA varied from a max between 0300 and 0400 hr to a minimum at 1500 hr. Results indicate that intestinal toxicity of 5-FU may be minimized by controling the time of injections. (35 Refs)

16. CHANGES IN TOXIC AND ANTITUMOR PROPERTIES OF FTORAFUR BY INDUCTION OR INHIBITION OF THE MICROSOMAL ENZYMES ACTIVITY.

Belitsky GA, Bukhman VM, Konopleva IA
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Cancer Chemother Pharmacol; 6(2):183-187 1981

The effect of the microsomal enzyme inducers phenobarbital (PB) and 20-methylcholanthrene (MC) and the system inhibitor SKF 525A on toxic effects produced by ftorafur (FT) and FT antitumor activity were determined. A single FT dose of 300 mg/kg caused lethargy lasting 5-20 hr in B6 mice. Pretreatment of animals with inducers of microsomal enzymes diminished this complication, the highest antilethargic effect was registered in the case of concurrent PB and MC injections. In contrast, administration of SKF 525A increased duration of the FT-induced neurotoxic reaction 3-4x, with some mice dying on day 1. At the dose administered, SKF 525A inhibited the antilethargic action of the inducers, its action was least marked against the PB plus MC combination. With regard to the delayed toxic action of FT, 100% of B6 mice pre-inoculated with PB and MC died with a FT dose as low as 200 mg/kg. SKF 525A (50 mg/kg) inhibited the delayed toxic effect of PB plus FT, but not that of FT and MC. Pretreatment of mice with PB and MC intensified the effect of FT on Rauscher leukemia cells. CBAB6F1 mice bearing hemangiopericytoma were more tolerant of FT and could tolerate high FT doses. Without additional effects, FT (600 mg/kg) inhibited the growth of hemangiopericytoma; this dose appeared toxic. After PB pretreatment, considerable inhibition of tumor growth was observed with as little as 300 mg FT/kg, and the antitumor and delayed toxic effects of 400 mg/kg FT were equal to those of 600 mg/kg without enzyme induction. Leukemia La was also markedly resistant to FT. Max effect was achieved at FT dose of 200 mg/kg, and at 100 mg/kg after PB pretreatment. The combination of PB, MC, and FT exhibited marked antitumor activity even at 50 mg FT/kg. SKF 525A did not stimulate the FT antitumor action at low doses. (29 Refs)

17. ALTERATION OF GALLIUM-67 DISTRIBUTION IN TUMOR-BEARING MICE FOLLOWING TREATMENT WITH METHOTREXATE: CONCISE COMMUNICATION.

Chilton HM, Witcofski RL, Watson NE, Heise CM
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J Nucl Med; 22(12):1064-1068 1981

The effect of methotrexate (MTX) treatment upon Ga-67 distribution was investigated. Tumor bearing mice were injected with Ga-67 citrate at varying time intervals following MTX treatment administered either as a single dose or in multiple doses. Altered Ga-67 distribution was observed following MTX therapy, the general pattern showing decreased levels in blood and increased uptake in bone. MTX therapy decreased Ga-67 uptake in liver, tumor, and muscle. The effects of MTX are related to the dose and time interval between the administrations of MTX and Ga-67. The serum of MTX-treated mice had lower unsaturated iron binding capacities and higher levels of unbound Ga-67. Serum iron and iron binding in rats determined 20 hr after MTX therapy showed significantly higher levels of serum iron and lower levels of Ga-67 in blood, and the percent transferrin saturation was approximately 95%. These observations suggest that MTX inhibition of erythropoiesis elevates serum iron levels and decreases the availability of gallium-binding sites in serum, resulting in altered Ga-67 tissue distribution. (Author abstract) (19 Refs)

18. EFFECT OF CYCLOPHOSPHAMIDE ON BONE MARROW OF BANK VOLES.

Domareva OP, Samokhvalova NS
A. N. Severtsov Inst. Evolution Morphology and Animal Ecology, Moscow, USSR
Genetika; 17(9):1639-1643 1981

The administration of cyclophosphamide (0.05 mg/g, ip) to bank voles increased the yield of chromosome aberrations. A max number of aberrant cells was observed 6 hr after the drug was administered. (16 Refs) (In RUS)

19. COMMON TOXIC EFFECTS OF SYSTEMIC DRUGS ON THE EYE.

Bryant WM
Wills Eye Hosp., Philadelphia, PA
Occup Health Nurs; 29(6):15-17 1981

Systemically administered drugs may affect the eyelids, conjunctiva, tear film, cornea, uveal tract, lens, retina, and optic nerve. Methotrexate and related antimetabolites and 5-fluorouracil (5FU) have effects upon the conjunctiva. Tamoxifen may have effects on the cornea and retina. Prolonged corticoid administration may produce cataracts. Oral contraceptives may have effects on the retina (vascular thrombosis) and may contribute to optic neuritis. (16 Refs)

20. SUMMARY AND PROSPECTIVE STATEMENT CONCERNING THE GENITOURINARY WORKSHOP.

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Joint Cancer Center, Boston, MA, 02115
Cancer Clin Trials; 4(Suppl):25-29 1981

The acute and chronic effects of chemotherapy and radiation treatment on the genitourinary (GU) tract are reviewed. The late effects of radiotherapy on the bladder include chronic cystitis, hematuria, and contracted bladder. Late effects of radiation on the prostate can include obstruction, incontinence, and impotence. Renal complications have been shown to occur with cis-Pt, streptozotocin, and high-dose methotrexate. Betamicroglobulin and beta-glucuronidase are being investigated for their potential in evaluating nephrotoxicity. Recommendations for the future identification and evaluation of the late effects on the GU system include the development of a prospective and retrospective surveillance system, the careful evaluation of renal function, size, and pathology at long intervals after cancer treatment, the study of all possible GU effects of new and established antitumor agents, the monitoring of the pharmacology and drug interaction of antitumor agents, and the establishment of a 5-point scoring system for the magnitude of the late effects. (19 Refs)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

21. CYTOTOXICITY OF A NEW URIDINE ANALOG, 4-HYDROXY-1-(BETA-D-RIBOFURANOSYL)PYRIDAZIN-6-ONE, AND ITS INTERACTION WITH URIDINE KINASE.

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(c/o Wotring) Coll. Pharmacy, Univ. Michigan, Ann Arbor, MI, 48109
Cancer Res; 42(1):100-106 1982

A new uridine analog, 4-hydroxy-1-(beta-D-ribofuranosyl)pyridazin-6-one (3-deaza-6-azaUrd), inhibited the growth of L1210 cells in culture, with a concentration to reduce growth rate to 50% of control of 7 x 10(-5) M. After treatment for 24 or 48 hr with 5 x 10(-4) M 3-deaza-6-azaUrd, 80% of the cells were unable to resume growth when the analog was removed from the cultures; also, 99% of the cells were killed, as determined by colony formation in soft agar. Studies on the prevention of the cytotoxic effects of 5 x 10(-4) M 3-deaza-6-azaUrd showed that uridine or cytidine gave complete protection. 2'-Deoxycytidine also gave partial protection, but orotic acid or thymidine had no effect on the growth inhibition by 3-deaza-6-azaUrd. These results suggested that growth inhibition by 3-deaza-6-azaUrd might be due to interference in pyrimidine biosynthesis. Activation of 3-deaza-6-azaUrd to its 5'-phosphate derivative appeared to be catalyzed by uridine kinase. 3-Deaza-6-azaUrd was shown to be catalyzed by uridine kinase. 3-Deaza-6-azaUrd was shown to compete with uridine for phosphorylation (Ki = 4.7 mM) and, therefore, to be a possible alternative substrate for uridine kinase from mouse kidney (Km for uridine = 82 uM). The enzyme was partially purified by streptomycin sulfate precipitation, ammonium sulfate fractionation, and gel filtration. This preparation was found to be free of pyrimidine nucleoside phosphorylase and uridine monophosphate kinase. (Author abstract) (30 Refs)

22. SYNTHESIS AND EVALUATION OF GUANAZOLE PRODRUGS AS ANTINEOPLASTIC AGENTS.

Dias Selassie C, Lien EJ, Khwaja TA
Section Biomedicinal Chemistry, Univ. Southern California, Los Angeles, CA, 90033
J Pharm Sci; 70(11):1281-1283 1981

Nine amide derivatives of guanazole were synthesized, and eight of them were tested for antineoplastic activity versus L1210 cells in vitro. Several of these compounds exhibited activity comparable to or greater than that of guanazole. (Author abstract) (8 Refs)

23. PYRAN COPOLYMER AND 7,12-DIMETHYLBENZANTHRACENE-INDUCED CARCINOGENESIS IN THE HAMSTER CHEEK POUCH.

Gould AR, Miller CH, Kafrawy AH
Dept. Oral Pathology/Pathology, Univ. Louisville, Health Sciences Center, Sch. Dentistry, Louisville, KY, 40292
Arch Oral Biol; 26(10):761-767 1981

The anticarcinogenic action of pyran copolymer (PC) on 7,12-dimethylbenzanthracene (DMBA)-induced carcinogenesis in the cheek pouch of male Golden Syrian hamsters was examined. All hamsters treated topically with DMBA exhibited buccal pouch tumors after 11 wk. None of the animals receiving no treatment (Group 1) or mineral oil alone (Groups 2 and 4) developed tumors. Group 3 (saline- and DMBA-treated) and

Group 5 (PC- and DMBA-treated) hamsters displayed mean tumor latent periods of 7.900 and 8.074 wk, respectively. Groups 3 and 5 exhibited mean tumor diameters of 2.7 and 3.0 mm, respectively, at 11 wk. Groups 1-4 included 6 hamsters each; Group 5 was composed of 24 hamsters. One hamster each in groups 1, 2, 3, and 5 died prior to the end of the 11-wk period. No significant difference in carcinoma incidence was observed between Groups 3 and 5 after 11.5 wk. Of Group 3 and 5 hamsters, 100% and 96%, respectively, developed carcinomas. No consistent difference in histologic appearance of carcinomas was observed between Groups 3 and 5. Mean hemagglutinin titers were higher in groups receiving PC than in the saline-treated control groups, but the difference was not significant. Analysis of immunologic findings for Groups 3 and 5 demonstrated a statistically significant difference in respective mean titers ($p = 0.01$). Organ and blood-cell changes were noted only in PC-treated animals. The results indicated that PC had little if any effect on DMBA-mediated buccal pouch carcinogenesis. (27 Refs)

24. TRISARUBICINOL, NEW ANTITUMOR ANTHRACYCLINE ANTIBIOTIC.

Yoshimoto A, Matsuzawa Y, Matsushita Y, Oki T, Takeuchi T, Umezawa H
Central Res. Lab., Sanraku-Ocean Co., Ltd., 4-9-1 Johnan, Fujisawa 251, Japan
J Antibiot (Tokyo); 34(11):1492-1494 1981

The microbial glycosidation of carminomycinone and 13-dihydrocarminomycinone by the mutant Streptomyces galilaeus strain KE303 yielded trisarubicinol. Characterization of trisarubicinol included elucidation of physicochemical properties, paramagnetic resonance spectrum, and antitumor activity against leukemia L1210 in CDF1 mice. (6 Refs)

25. FREDERICAMYCIN A, A NEW ANTITUMOR ANTIBIOTIC. II. BIOLOGICAL PROPERTIES.

Warnick-Pickle DJ, Byrne KM, Pandey RC, White RJ
Chemotherapy Fermentation Program, Frederick Cancer Res. Center, Post Office Box B, Frederick, MD, 21701
J Antibiot (Tokyo); 34(11):1402-1407 1981

Fredericamycin A is a novel antibiotic produced by a soil isolate of Streptomyces griseus (FCRC-48). In vitro, fredericamycin A exhibits antibacterial, antifungal, and cytotoxic activities. In vivo, fredericamycin A exhibits very good antitumor activity against P388 mouse leukemia as well as the CD8F mammary tumor and marginal activity against B16 melanoma. Fredericamycin A failed to demonstrate any interaction with DNA and inhibited protein and RNA synthesis preferentially to DNA synthesis in Bacillus subtilis and P388 cells. (Author abstract) (11 Refs)

26. NEW DIMERIC ANALOGUES OF ETHIDIUM: SYNTHESIS, INTERACTION WITH DNA, AND ANTITUMOR ACTIVITY.

Kuhlmann KF, Mosher CW
Bio-Organic Chemistry Lab., SRI International, Menlo Park, CA, 94025
J Med Chem; 24(11):1333-1337 1981

Three new dimeric analogues of ethidium cation in which the monomeric moieties are linked at the 3' positions by alpha,omega-diethers of varying length and composition have been synthesized. The circular dichroism spectra of all three compounds indicate that they double intercalate, and their effects on the thermal helix-coil transition profile of poly(dA-dT) show extremely high affinity for helical DNA, with details of the binding interaction depending on the length and composition of the connectin g chain. The ability of the compounds to inhibit nucleic acid synthesis in L1210 cell culture also differed significantly, as did their antitumor effects against P388 leukemia and B16 melanoma. Compound 2, with 10 methylene groups in the connecting chain, 5-20 x as potent as ethidium against murine P388 leukemia. These results clearly illustrate the advantage gained by incorporating a weak antitumor agent in a double-intercalating analogue. (Author abstract) (22 Refs)

27. CYTOKINETIC AND BIOCHEMICAL EFFECTS OF SANGIVAMYCIN IN HUMAN COLON CARCINOMA CELLS IN CULTURE.

Glazer RI, Hartman KD
NCI, Building 37, Rom 6D28, Bethesda, MD
Mol Pharmacol; 20(3):657-661 1981

The cytokinetic and biochemical effects of sangivamycin (SG) on human colon carcinoma in tissue were studied. Log phase and early plateau phase cells were exposed for 2, 24, and 48 hr to SG and cell viability was determined by soft agar cloning. Brief (2 hr) drug exposure of either log- or plateau-phase cells was not cytotoxic. Prolonging drug exposure to 24 or 48 hr dramatically increased cell lethality; 1 x 10(-6) M SG reduced cell viability of log phase cells by 83% and 97% after 24 and 48 hr of drug exposure, respectively, while cell viability was reduced in plateau-phase cells by 20% and 75%, respectively. Increasing the SG concentration to 1 x 10(-5) M increased cytoxicity only in plateau-phase cells. DNA synthesis was not significantly affected after 2 hr of drug exposure, but precipitously decreased following prolonged incubation with SG for 24 or 48 hr. In contrast, total RNA synthesis was initially inhibited up to 40% after 2 hr of exposure to 1 x 10(-5) SG, but was not reduced much further after longer intervals of drug treatment. RNA synthesis was not significantly inhibited in plateau-phase cells after 48 hr of drug exposure. In contrast, inhibition of non-poly(A)RNA and poly(A)RNA occurred to a degree comparable to that of total RNA in log-phase cells. The time and concentration dependence of SG incorporation into DNA and RNA correlated qualitatively with the effect of SG on cell viability. The incorporation of 3H-SG into poly(A)RNA correlated with the reduction in cell viability observed in log- and plateau-phase cells under comparable conditions. Results indicated that SG produces significant cell lethality to a human colon carcinoma which is generaly refractory to antitumor agents. (15 Refs)

28. ANTITUMOR AGENTS. 49. TRICIN, KAEMPFEROL-3-O-BETA-D-GLUCOPYRANOSIDE AND (+)-NORTRACHELOGENIN, ANTILEUKEMIC PRINCIPLES FROM WIKSTROEMIA INDICA.

Lee KH, Tagahara K, Suzuki H, Wu RY, Haruna M, Hall IH, Huang HC, Ito K, Iida T, Lai JS
Dept. Medicinal Chemistry, Sch. Pharmacy, Univ. North Carolina, Chapel Hill, NC, 27514
J Nat Prod; 44(5):530-535 1981

Active principles of Wikstroemia indica (Thymelaeaceae) were isolated by column chromatography of the active final chloroform extract on silica gel. Isolation led to the characterization of tricin, kaempferol-3-O-beta-D-glucopyranoside and (+)-nortrachelogenin as the major antileukemic constituents. Daphnoretin was identified as the potent antitumor principle against Ehrlich ascites carcinoma growth in mice. (21 Refs)

29. USE OF AN HFR STRAIN OF E. COLI FOR PRESCREENING OF ANTITUMOR ANTIBIOTICS.

Tanida S, Hasegawa T, Yoneda M
Microbiological Res. Lab., Central Res. Div., Takeda Chemical Industries, 17-85, Juso-honmachi 2-chome, Yodogawa-ku, Osaka 532, Japan

Agric Biol Chem; 45(9):2013-2018 1981

An assay system with the Escherichia coli strain Hfr was examined for its ability to detect new antibiotics interacting with DNA. The screening system was established by the paper disc method at 42 and 32 C, using TE 120 and TE 144. Thirty antibiotics and five chemicals were tested. Some of the agents showed preferential activity against TE 120 at 42 C; however, some agents known to bind to DNA strands showed no activity. Nocardia sp. No C-14919 (N-1001) produced active metabolites which were new aminobenzoquinoid antibiotics, named dnacins. Dnacins showed preferential activity against the Hfr strain at high temperature in an aqueous condition. Dnacins A1 at 0.1 ug/ml and B1 at 0.05 ug/ml suppressed the growth of TE 120 at 42 C; twice the amount of each component did not markedly affect growth of TE 144 at 42 C. Thus, dnacins might show preferential activity against the replication machinery of F-like plasmids at effective concentrations. Dnacin B1 and dnacin A1 (0.05-0.1 ug/ml) caused a high frequency of plasmid loss from R 100-1 or F' gal-bearing strains without affecting growth of the host cells. The findings demonstrate that agents which interact with DNA are efficiently detected by the assay system. The relative inactivity of certain antibiotics may be explained by the permeability barrier of the test strain. (13 Refs)

30. METHOTREXATE ANALOGUES. 14. SYNTHESIS OF NEW GAMMA-SUBSTITUTED DERIVATIVES AS DIHYDROFOLATE REDUCTASE INHIBITORS AND POTENTIAL ANTICANCER AGENTS.

Rosowsky A, Forsch R, Uren J, Wick M
Dept. Pharmacology, Sidney Farber Cancer Inst., Boston, MA, 02115

J Med Chem; 24(12):1450-1455 1981

The gamma-tert-butyl ester, gamma-hydrazide, gamma-n-butylamide and gamma-benzylamide derivatives of methotrexate (MTX) were synthesized from 4-amino-4-deoxy-N(10)-methylpteroic acid (APA) and the appropriate blocked L-glutamic acid precursors with the aid of the peptide bond forming reagent diethyl phosphorocyanidate. The affinity of these side chain modified products for dihydrofolate reductase from Lactobacillus casei and L1210 mouse leukemic cells was determined spectrophotometrically or by competitive radioligand binding assay, and their cytotoxicity was evaluated against L1210 leukemic cells in culture. The results provide continuing support for the view that the 'gamma-terminal region' of the MTX side chain is an attractive site for molecular modification of this anticancer agent. (Author abstract) (28 Refs)

31. ANTITUMOR ACTIVITY OF 3-NITROSO-2-OXAZOLIDONES.

Miyahara M, Miyahara M, Kamiya S, Maekawa A
Natl. Inst. Hygienic Sciences, 1-18-1 Kamiyoga, Setagaya, Tokyo, 158, Japan

Chem Pharm Bull (Tokyo); 29(8):2366-2369 1981

Antitumor activity of 2-oxazolidones in cyclic carbamate form and of their N-nitroso derivatives was tested. Some 3-nitroso-2-oxazolidones were active against rat ascites hepatoma AH13 and mouse lymphoid leukemia L1210; their alkylating activities were involved in the antitumor mechanism. 2-Oxazolidones were all inactive against AH13 and L1210; the compounds were not toxic to Donryu rats and CDF1 mice at the max dose tested (250-500 mg/kg in rats and 400 mg/kg in mice). Some 3-nitroso-2-oxazolidones were active against AH13 and/or L1210. Ethyl N-ethyl-N-nitrosocarbamate, 1-ethyl-1-nitrosourea, and the cyclic nitrosourea 1-nitrosourea-2-imidazolidone were tested for antitumor activities against both tumors. The cyclic nitroso compounds appeared to have a stronger antitumor effect and to be more toxic than corresponding acyclic nitroso compounds. Reactions of the nitroso and non-nitroso compounds were compared by a method using the 4-(p-nitrobenzyl) pyridine reagent. The non-nitroso compounds did not give any color reaction, but the nitroso compounds gave a purple color. The results suggest that the nitroso compounds are alkylating agents. No correlation was found between antitumor activity and color intensity. (11 Refs)

32. CHEMOTHERAPEUTIC TRIALS WITH HAMSTER MESOTHELIOMA 10-24: RESPONSES TO AZACITIDINE, AZIRIDINYLBENZOQUINONE, CISPLATIN, AND PCNU.

Holiat SM, Smith WE, Hubert DD, Davis S
(c/o Davis) Oncology/Hematology, Veterans Admin. Medical Center, East Orange, NJ, 07019

Cancer Treat Rep; 65(11/12):1113-1115 1981

Asbestos-induced peritoneal mesothelioma 10-24 serially transplanted in Syrian golden hamsters was used to test responses to seven drugs as single agents. Compared to saline-treated controls, the av survival time increased 51%-85% with azacitidine, 42%-60% with aziridinyl-benzoquinone, 43% with cisplatin, and 35%-45% with PCNU. No cures were achieved. Therapeutic responses were not observed with dactinomycin, dianhydroxyanthracenedione, or DTIC. (Author abstract) (4 Refs)

33. COMBINED ACTION OF CHROMIUM AND NICKEL ON MOUSE AND HAMSTER FIBROBLAST CELL LINES.

Rossner P, Bencko V, Sram RJ
Inst. Hygiene and Epidemiology, Srobarova 48, 100 42 Praha 10, Czechoslovakia

J Hyg Epidemiol Microbiol Immunol; 25(3):252-258 1981

Cytotoxic effects of trivalent Cr(III) and hexavalent Cr(VI) chromium and bivalent nickel Ni(II) and of their combinations were tested on suspension cultures of mouse fibroblast line L-A 115. Cytogenetic analysis was performed on the Chinese hamster cell strain 237-2a. Hexavalent chromium (10(-3)-10(-5) M) was lethal for mouse fibroblasts. Concentrations 10(-6) M and 10(-7) M produced considerable cell growth inhibition. Trivalent chromium ions (10(-3)-10(-6) M) had no influence on cell growth. Bivalent nickel ion (10(-3) M) was lethal; 10(-4) M concentrations inhibited cell growth by approx 25%. The combination of two non-toxic concentrations, 10(-5) M Ni(II) and 10(-3) M Cr(III), produced approx 50% growth inhibition. Cytogenetic analysis of Chinese hamster cells revealed a linear correlation between the number of detected aberrant cells and the applied concentration of bivalent nickel and trivalent chromium ions [Ni(II) 10(-5)-10(-7) M; Cr(III) 10(-3)-10(-5) M]. After exposure to the combination Ni(II) 10(-5) M x Cr(III) 10(-3) M which was inhibitory to cellular growth, only simple summation of actions occurred. A similar result was obtained after exposure to the combination at a lower concentration Ni(II) 10(-7) M x Cr(III) 10(-5) M. In contrast, after the Ni(II) 10(-6) M x Cr(III) 10(-4) M combination the number of induced aberrations was significantly ($p = 0.01$) lower than that anticipated after summation of actions; the phenomenon may result from stimulation of cellular repair mechanisms. (10 Refs)

34. ANTICANCER AGENTS--XVI. SYNTHESIS AND CYTOTOXICITY OF SOME 5-ARYLAZO-4,6-DIMETHYLPYRIMIDINES.

O'Sullivan JF
Lab., Medical Res. Council Ireland, Trinity Coll., Dublin 2, Ireland
Proc R Ir Acad [B]; 81(1):1-4 1981

Concentrations at which 17 arylazopyrimidines inhibited HeLa cell growth by 50% are listed. Twelve of the compounds were active against HeLa cells, but none showed in vivo activity against P388 lymphoid leukemia or Ehrlich tumors in mice. (5 Refs)

35. BROMOCRIPTINE: PRESENT AND FUTURE CONSIDERATIONS.

Guay AT
Section Endocrinology and Metabolism, Lahey Clinic, Boston, MA
Lahey Clin Found Bull; 30(1):24-27 1981

The actions, indications, results, mode of administration, adverse reactions, and potential uses of bromocriptine (BR) are discussed. BR shows the most promise among all drugs tested in recent yr for the effective medical treatment of pituitary tumors which cause acromegaly. (5 Refs)

36. INHIBITORY EFFECTS OF FOUR ISOABRINS ON THE GROWTH OF SARCOMA 180 CELLS.

Lin JY, Lee TC, Tung TC
Dept. Biochemistry, Coll. Medicine, Natl. Taiwan Univ., Taiwan, Republic of China
Cancer Res; 42(1):276-279 1982

The four isoabrins were shown to be capable of inhibiting the growth of tumor cells in vivo when one-fifth of their median lethal dose was used. From the in vitro experiments, the doses required for 50% inhibition of protein biosynthesis are 3.2 pg, 45 ng, 32 ng, and 10 ng/ml for abrin-a, -b, -c, and -d, respectively. Except for abrin-b, a good correlation between the inhibitory effects of abrins on the tumor growth and protein biosynthesis was observed. These isoabrins show a moderate inhibitory effect of DNA biosynthesis. (Author abstract) (19 Refs)

STUDIES OF ANTIMETASTATIC AGENTS

37. ANTICOAGULANTS AND EXPERIMENTAL METASTASES: EVALUATION OF ANTIMETASTATIC EFFECTS IN DIFFERENT MODEL SYSTEMS.

Maat B, Hilgard P
Radiobiological Inst., TNO, Rijswijk, Brugstraat 10, 5042 SB-Tilburg, The Netherlands
J Cancer Res Clin Oncol; 101(3):275-283 1981

The ability of the anticoagulants ancrod (AN), heparin (HP), and phenprocoumon (PPC) anticoagulants to produce antimetastatic effects in iv tumor systems (Lewis lung (3LL) carcinoma and B16 melanoma) and to reduce spontaneous metastases was studied. After iv injection of tumor cells into C57BL/Rij mice, a significant decrease of the number of lung colonies was found in mice pretreated with AN as compared to control animals. Continued AC did not decrease the number of lung metastases as compared to controls in either system. The mean blood coagulation times of 11 AC-treated animals were 10.4 min. Continued HP treatment was similarly unable to diminish the numbers of metastases in C57BL/Rij mice bearing sc transplanted tumors. The number of metastases was equal in HP-treated and control groups of both tumor systems. The size of the respective lung colonies or metastases did not differ significantly in the various experimental groups as compared to controls. In addition, the amputated tumor-bearing leg of the HP group did not differ significantly from the corresponding control group. The The number of spontaneous metastases in the PPC-treated animals was significantly reduced in both tumor systems as compared to untreated control animals. The results suggested that the capacity of circulating malignant cells to form spontaneous metastases is not influenced by most drugs having strong anticoagulant properties. Coumarin derivatives seem to have strong antimetastatic capabilities. (44 Refs)

INTERFERON AND OTHER ANTIVIRALS

38. EFFECT OF 1,4-DIHYDROXY-5,8-BIS (2-(2-HYDROXYETHYLAMINO)ETHYL AMINO)-9,10-ANTHRACENEDIONE (DIHYDROXYANTHRAQUINONE) ON THE REPLICATION OF SIMIAN VIRUS 40 CHROMOSOME.

Su RT
Dept. Microbiology, Univ. Kansas, Lawrence, KS, 66045
Biochem Biophys Res Commun; 103(1):249-255 1981

Dihydroxyanthraquinone (DHAQ) is an aminoanthraquinone derivative with potential anticancer activity. While SV40 infection of both permissive and nonpermissive cells stimulates cellular DNA synthesis, the presence of 1.6 nanoM DHAQ inhibited by approx 50% both cellular and viral DNA synthesis. Nearly 90% inhibition was observed at DHAQ concentrations of 0.4 uM or higher. Both RNA and protein synthesis was inhibited 50% in the presence of 0.8-8 uM DHAQ, where DNA synthesis is inhibited by 90%. Results indicate that both cellular and viral chromosome replication are inhibited to the same extent in cells treated with low concentrations of DHAQ. No detectable change in sedimentation on sucrose gradients was observed in viral chromosomes isolated either from DHAQ-treated cells or incubated directly with DHAQ at 2-10 uM. Aggregation of viral chromosomes occurred when very high DHAQ concentrations were used (greater than 20 uM). (21 Refs)

39. DIFFERENTIAL EFFECT OF IMIDAZOLE ANTIBIOTICS ON UNTRANSFORMED AND VIRUS-TRANSFORMED RAT CELL LINES.

Kuwano M, Akiyama S, Kaneko M, Ikezaki K, Takuki R, Kimura G
Dept. Biochemistry and Internal Medicine, Oita Medical Sch., Hazama-cho, Oita 879-56, Japan
Cancer Res; 42(1):280-284 1982

The imidazole antimycotics clotrimazole and miconazole were tested on untransformed rat cell line 3Y1-B clone 1-6 (3Y1) and six transformed cell lines, which were independently isolated from 3Y1 or 3Y1-B clone 1 after infection with adenovirus 12 (AD-12) or with SV40, to determine their sensitivities to these drugs. The relative plating efficiency of three cell lines (T3, W4, and W5) transformed with AD-12 was reduced to 10(-1) of the initial value by clotrimazole (2 to 4 ug/ml), whereas that of the parental cell line 3Y1 was reduced to 10(-1) of the initial value by clotrimazole (20 to 25 ug/ml). By contrast, the differential effect of miconazole on 3Y1 and AD-12-

transformed cell lines was found to be a factor of 2. The sensitivity of the SV40-transformed cell lines to these drugs was between the untransformed 3Y1 and the AD-12-transformed cell lines. The cellular sensitivity of untransformed 3Y1 cells to clotrimazole was significantly enhanced when exposed to various doses of the unsaturated fatty acid, linoleic acid. The untransformed and transformed cell lines showed sensitivities similar to the cytocidal activity of sterol-binding antimycotics, amphotericin B, and filipin. (Author abstract) (30 Refs)

40. INHIBITION OF CELLULAR AND VIRUS-ASSOCIATED NUCLEOTIDE POLYMERASES BY, AND ANTI-HERPES SIMPLEX VIRUS ACTIVITY OF, STREPTOVARICIN DERIVATIVES.

Srivastava BI, DiCioccio RA, Chadha KC, Rinehart KL
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY, 14263
Antimicrob Agents Chemother; 20(5):653-659 1981

Fourteen streptovaricin derivatives were tested for inhibition of cellular nucleotide polymerases (DNA polymerase alpha, DNA polymerase beta, and DNA polymerase gamma, terminal deoxynucleotidyltransferase [TdT], and RNA polymerase II), simian sarcoma virus deoxyribonucleic acid polymerase, and herpes simplex virus Type 1-induced deoxyribonucleic acid polymerase (HSV-DP). Three compounds (streptovadienal C, prestreptovarone, and streptoval Fc) preferentially inhibited TdT and HSV-DP over the other enzymes. These compounds inhibited HSV-DP more potently than they inhibited TdT. Evidence indicated that the mode of inhibition of TdT and HSV-DP by streptovadienal C and prestreptovarone was by interaction with the enzymes and not with template-primer, initiator, substrates, or divalent cations required for enzyme activity. Furthermore, data suggested that these compounds bind with greater affinity to HSV-DP than to TdT. Streptovadienal C and prestreptovarone were examined for their effect on the replication of herpes simplex virus Type 1 in African green monkey kidney (CV1) cells. These compounds produced 2-and 3-log drops in virus titer, respectively, at concentrations not significantly affecting cell viability. This correlated with evidence indicating a greater binding affinity of these compounds for HSV-DP over cellular nucleotide polymerases. (Author abstract) (27 Refs)

41. ANTITUMOR ACTIVITY OF 5-HYDROXYMETHYL-2-FUROIC ACID.

Munekata M, Tamura G
Res. and Development Lab., Sapporo Breweries Ltd., Mita, Meguro-ku, 153, Tokyo, Japan
Agric Biol Chem; 45(9):2149-2150 1981

The compound 5-Hydroxymethyl-2-furoic acid (65-I) has been isolated from the ethylacetate extract of the cultured broth and mycelium of Pyricularia grisea IAM 5051. The compound was shown to have selective cytotoxicity against Simian virus 40 (SV40)-transformed cells in vitro and antitumor activity against Sarcoma 180 in vivo. The isolation procedure and physical characteristics of 65-I are described. The compound had selective toxicity against SV40-transformed C3H-2K cells from day 1 at concentrations from 125 to 2,000 ug/ml; the minimum cytotoxic concentration increased with treatment time. The total packed cell vol (TPCV) method was used to assay antitumor activity in vivo. Ascitic tumor cells of sarcoma 180 were implanted ip in ICR mice (5 wk old, 17.5-20 g). Saline soln of the samples was administered 1x/day for 5 consecutive days (50 mg/kg x 5). The vol of tumor cells in ascites was measured on day 7. The ratio of TPCV of the test group to that of the control group was 36.6; antitumor activity was judged effective. (2 Refs)

42. NORMAL AND FRIEND VIRUS SPECIFIC CELL COMPARTMENTS IN FRIEND LEUKEMIA CHARACTERIZED BY THEIR SENSITIVITY TO ACTINOMYCIN D IN VIVO.

Seidel HJ, Kreja L, Opitz U, Steinheider G, Eberle P
Abteilung fur Klinische Physiologie und Arbeitsmedizin, Universitat Ulm, Oberer Eselsberg M24, D-7900 Ulm, W. Germany
Blut; 43(5):287-296 1981

The sensitivity to actinomycin D (Act D) of the erythropoietin (EP)-independent erythropoiesis after polycythemia-inducing Friend virus (F-MuLV-P) infection of DBA/2 mice, especially of erythroid erythropoietic burst forming units (BFU-E), infectious centers producing cells (ICPC), and CFU- EI, a late erythroid stem cell corresponding to normal erythroid colony forming unit (CFU-E) but independent of Ep, was examined and compared to that of normal erythropoiesis. Fifteen ug/kg Act D had no effect on spleen wt and reticulocytosis, while 30 ug/kg reduced reticulocyte number and marginally affected spleen wt. Three and five doses of 60 ug/kg Act D completely suppressed reticulocytosis. In control animals, all CFU-E were Ep independent. After Act D treatment, no colony growth was seen for 3 days; then regeneration began, overshooting in the femur at day 5. All colony growth was Ep independent. Act D reduced ICPC numbers in the spleen to less than 1/10, mainly to due to the reduced spleen cellularity. Five doses of 60, 30, and 15 ug/kg Act D showed a dose-dependent reduction of CFU-E numbers in the femur and spleen. Spleen ICPC was sensitive to 5 x 60 ug/kg and possibly to 5 x 30 ug/kg. The max reduction was only about 10-fold, corresponding to reduction in organ size. The study of femur ICPC showed day-to-day variability. In comparison to normal uninfected mice, the number of stem cell (CFU-S) and culture (CFU-C) colony forming units was slightly lower in the femur of F-MuLV-P-infected mice. After Act D treatment, CFU-S and CFU-C were not significantly influenced, while the number of BFU-E increased at day 1 and 5 and was below virus-infected control at day 8. It was concluded that BFU-E were not affected in the bone marrow by Act D and showed some sensitivity in the spleen, since the rise in BFU-E concentration was not high enough to compensate for reduction in organ size. (21 Refs)

43. INTERFERON-MEDIATED DEPRESSION OF CYTOCHROME P-450-DEPENDENT DRUG BIOTRANSFORMATION.

Singh G, Renton KW
(c/o Renton) Dept. Pharmacology, Dalhousie Univ., Sir Charles Tupper Medical Building, Halifax, Nova Scotia B3H 4H7, Canada
Mol Pharmacol; 20(3):681-684 1981

The relationship between depression of hepatic cytochrome P-450 by Newcastle disease virus (NDV) and circulating interferon (IF) levels was studied in inbred strains of C3H/HeJ and C57BL/6J carrying the high (IF-1h) and low (IF-1l) production allele at the IF-1 locus. Twenty-four hr after the administration of NDV to C57BL/6J mice carrying the IF-1H allele, the mean circulating level of IF was 2,443 PRD50 units (amount of IF required for 50% plaque reduction). At the same time, cytochrome P-450 levels and aminopyrine N-demethylase (APDM) levels were depressed by 35% and 48%, respectively, in hepatic microsomes. In C3H/HeJ mice carrying the IF-1l allele, the circulating levels of IF were below the lowest limit of detection 24 hr after NDV treatment. In these mice, NDV had no effect of cytochrome P-450 or APDM activity levels. Twenty-four hr after the administration of poly(rI-rC), which induces IF formation via loci other than IF-1, high concentrations of IF were observed in the sera of both strains of mice. In C57BL/6J mice, cytochrome P-450 and and APDM activities were decreased by 44% and 50%, respectively, 24 hr after poly(rI-rC). In C3H/HeJ mice, cytochrome P-450 and APDM activities were decreased by 33% and 38% following poly(rI-rC) administration. In both strains, cytochrome b5 was unchanged following poly(rI-rC) treatment. It was concluded that an impairment of P-450-mediated drug biotransformation occurs via an IF-mediated interaction and that this effect may enhance the toxicity of drugs and exogenously administered chemicals. (20 Refs)

OTHER RELATED STUDIES

44. STABILITY AND COMPATIBILITY OF ANTITUMOR AGENTS IN GLASS AND PLASTIC CONTAINERS.

Benvenuto JA, Anderson RW, Kerkof K, Smith RG, Loo TL

Dept. Developmental Therapeutics, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030

Am J Hosp Pharm; 38(12):1914-1918 1981

The stability of methotrexate, fluorouracil, cytarabine, dactinomycin, doxorubicin, bleomycin sulfate, mitomycin, mithramycin, vincristine sulfate, vinblastine sulfate, cyclophosphamide, dacarbazine, carmustine, and leucovorin calcium in underfilled plastic and glass administration containers was determined. Drugs were reconstituted according to manufacturers' instructions and added to 5% dextrose injection 50 ml in both polyvinyl chloride bags and glass partial-fill bottles. In addition, mitomycin was added to 0.9% sodium chloride injection 50 ml in both polyvinyl chloride bags and glass partial-fill bottles. All admixtures were stored at room temperature, not protected from light. Stability was determined over 24 hr (48 hr for doxorubicin and fluorouracil) by high-pressure liquid chromatography, except cyclophosphamide (analyzed by mass spectrometry) and carmustine (analyzed by spectrophotometry). Methotrexate, leucovorin calcium, cytarabine, dactinomycin, mithramycin, vinblastine sulfate, cyclophosphamide, and dacarbazine were equally stable (10% or less change in concentration over 24 hr) in glass and plastic containers. Doxorubicin and fluorouracil were more stable in plastic containers than glass containers. The T90 value for doxorubicin in glass was 40 hr; there was no apparent decrease in plastic even after 48 hr. The T90 value for fluorouracil in glass was 7 hr and in plastic, 43 hr. Vincristine sulfate, bleomycin sulfate, and carmustine were more stable in glass than plastic. The T90 value for vincristine sulfate in plastic was 10 hr. The T90 value for bleomycin sulfate in plastic was 0.7 hr. The T90 value for carmustine in plastic was 0.6 hr. Mitomycin dissolved in 0.9% sodium chloride injection was more stable in plastic. Mitomycin dissolved in 5% dextrose injection was not stable. Carmustine and bleomycin sulfate should be administered only in glass containers. Continuous infusions of doxorubicin and fluorouracil are more completely delivered from plastic containers. Mitomycin should not be dissolved in 5% dextrose injection. (Author abstract) (10 Refs)

45. PROPERTIES OF A METHOTREXATE-INSENSITIVE VARIANT OF DIHYDROFOLATE REDUCTASE DERIVED FROM METHOTREXATE-RESISTANT L5178Y CELLS.

Goldie JH, Dedhar S, Krystal G
Dept. Medicine, Univ. British Columbia, 2656 Heather St., Vancouver, B. C. V52Z 3J3, Canada
J Biol Chem; 256(22):11629-11635 1981

We have established the presence of two distinct forms of dihydrofolate reductase in methotrexate-resistant L5178Y lymphoma cells. It was previously found that one of the reductases (Form II) was approximately 100,000-fold more resistant to methotrexate inhibition than Form I. In this report, the two forms of dihydrofolate reductase have been partially purified and their properties have been compared. The two forms were found to differ markedly in their heat stability, isoelectric points, and sensitivity to p-chloromercuriphenyl sulfonate. There were, in addition, minor differences in their Km and Vmax for folic acid, their pH optima, and their mol wt. The loss of sensitivity to methotrexate inhibition by the Form II reductase is associated with significant alteration in the physical and chemical properties of the enzyme. (Author abstract) (37 Refs)

46. RESISTANCE TO THE CYTOCIDAL EFFECT OF ADRIAMYCIN IS AN EARLY PHENOTYPIC CHANGE INDUCED DURING HEPATOCARCINOGENESIS.

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Dept. Medical Oncology, City Hope Natl. Medical Center, 1500 E. Duarte Rd., Duarte, CA, 91010
Br J Cancer; 44(4):567-571 1981

Resistance to the cytocidal action of Adriamycin (ADR) was induced in rat hepatocytes by incorporation of the carcinogen 2-acetylaminofluorene into the rat diet. Using a quantitative assay in primary monolayer culture, it was demonstrated that resistance to ADR is an early phenotypic change that is induced during chemical carcinogenesis in the rat, and appears to be stable. (Author abstract) (20 Refs)

47. COMPARISON OF THE INHIBITION OF METHOTREXATE-SENSITIVE AND -RESISTANT LACTOBACILLUS CASEI CELL CULTURES WITH PURIFIED LACTOBACILLUS CASEI DIHYDROFOLATE REDUCTASE BY 4,6-DIAMINO-1,2-DIHYDRO-2,2-DIMETHYL-1-(3-SUBSTITUTED PHENYL)-S-TRIAZINES. USE OF QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS IN MAKING INFERENCES ABOUT THE MECHANISM OF RESISTANCE AND THE STRUCTURE OF THE ENZYME IN SITU COMPARED WITH THE ENZYME IN VITRO.

Coats EA, Genther CS, Dietrich SW, Guo ZR, Hansch C
Coll. Pharmacy, Univ. Cincinnati Medical Center, Cincinnati, OH, 45267
J Med Chem; 24(12):1422-1429 1981

The inhibitory action of a set of 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3-substituted phenyl)-2-triazines on Lactobacillus casei dihydrofolate reductase is compared with their action on methotrexate-resistant and methotrexate-sensitive cell cultures by means of quantitative structure-selectivity analysis. The analysis uncovers major differences in the steric and hydrophobic interactions of the substituents X with the three different systems. Correlation analysis is used to define the hydrophobic binding site for 3-X in the isolated enzyme. This is shown to be similar to that of the sensitive cells but different from that in the resistant cells, which have a larger hydrophobic binding site. When X has the general structure 3-CH2ZC6H4-Y (Z = O or NH), it is shown that Y does not interact with the isolated enzyme but in the living cells, Y interacts with a molecular barrier in a way that can be quantitatively related to the molar refractivity of X. The methotrexate-resistant cells are resistant to highly hydrophilic inhibitors such as methotrexate but are not able to resist hydrophobic inhibitors. The results with the inhibition of L casei dihydrofolate reductase are compared with the inhibition of enzyme from bovine liver. (Author abstract) (32 Refs)

48. SYNTHESIS OF 3-HYDROXYCYCLOPHOSPHAMIDE AND STUDIES RELATED TO ITS POSSIBLE ROLE IN THE METABOLISM OF CYCLOPHOSPHAMIDE.

Brandt JA, Ludeman SM, Zon G, Todhunter JA, Egan W, Dickerson R

Dept. Chemistry, Catholic Univ. America, Washington, DC, 20064

J Med Chem; 24(12):1404-1408 1981

Hydrogenolysis of 3-(benzyloxy)cyclophosphamide using Pd/C catalyst and ethyl acetate as solvent leads to the formation of 3-hydroxycyclophosphamide (3, approx 20%) and cyclophosphamide (1, approx 10%), accompanied by regioselective hydrogen-exchange reactions at the C-4 and C-5 positions in 3 and 1. A variety of oxidizing reagents and liver microsomal incubation failed to provide evidence (31P NMR) for conversion of 1 into 3, whereas identical incubation of 3 led to its reduction to 1. Compound 3 is stable at pH 6.5-8.2, 37 C, and exhibits anticancer activity comparable to 1 when tested against L1210 leukemia in mice. Data are discussed with regard to a previously reported suggestion that metabolism of 1 may involve oxidation to give 3 followed by rearrangement of 3 to 2. (Author abstract) (29 Refs)

49. 5-FLUORO- AND 5-CHLOROCYCLOPHOSPHAMIDE: SYNTHESIS, METABOLISM, AND ANTITUMOR ACTIVITY OF THE CIS AND TRANS ISOMERS.

Foster AB, Jarman M, Kinas RW, Van Maanen JM, Taylor GN, Gaston JL, Parkin A, Richardson AC

Mass Spectrometry-Drug Metabolism Group, Div. Chemistry, Inst. Cancer Res., London, SW3 6JB, England

J Med Chem; 24(12):1399-1403 1981

In seeking analogues of cyclophosphamide (1) having improved antitumor activity by virtue of accelerated formation of the cytotoxic metabolite phosphoramide mustard, cis and trans isomers of 5-fluoro- and 5-chlorocyclophosphamide (9,10,11, and 12, respectively) were synthesized by condensation of the appropriate 3-amino-2-halopropan-1-ol (13 or 26) with N,N-bis(2-chloroethyl)phosphoramidic dichloride (14). The metabolism of the halocyclophosphamides by rat liver microsomes was stereoselective; the cis isomers (9 and 11) were poorly metabolized, whereas the trans isomers (10 and 12) were metabolized with efficiency comparable to that of cyclophosphamide. However, there was no evidence that the yield of phosphoramide mustard produced by the trans analogues was significantly greater than that from cyclophosphamide following microsomal 4-hydroxylation. Hence, the halogen substituents did not accelerate Beta-elimination of acrolein from the acyclic aldehydo tautomers. As expected, the poorly metabolized cis-5-fluoride (9) had little activity against the ADJ/PC6 tumor in mice. However, the cis-5-chloride (11) was as active as the trans isomer (12) and each had approximately half the therapeutic index of 1. The trans-5-fluoride (10) was much less active, having an ED90 value some 16-fold that of 1. (Author abstract) (22 Refs)

50. DIURNAL VARIATIONS OF TUMOR GROWTH AND ITS INFLUENCE ON CYTOSTATIC TREATMENT.

Flentje M, Akokan G, Reinecke D, Klein HO

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Blut; 43(2):85-88 1981

Diurnal variations in Lewis lung carcinoma growth were studied in male C57Bl mice. The therapeutic effect of cyclophosphamide (CPA: 100 mg/kg, ip) administered at four different times with 6 hr intervals on day 5 after tumor transplantation was examined in relation to diurnal variations in tumor growth. Diurnal variations of tumor growth were observed. A minimum of DNA synthesizing activity was observed at 8:00 am. Thereafter, the activity increased up to a max between 8:00 and 12:00 pm. The results were statistically significant (p less than 0.01). Variations of the mitotic index were less distinct. These diurnal variations in tumor growth were not altered by abolition of light and dark periods. The therapeutic effect of CPA depended upon the day or night time of administration. The best results were obtained when CPA was injected at 8:00 am or 8:00 pm. Most of the mice were tumor-free macroscopicaly and microscopically when killed on day 90 after tumor transplantation. The results indicated the diurnal tumor growth characteristics may be important in the administration of antineoplastic agents. (7 Refs)

51. TOXICITY OF METHOTREXATE AND METOPRINE IN A DIHYDROFOLATE REDUCTASE GENE-AMPLIFIED MOUSE CELL LINE.

Hamrell M, Laszlo J, Brown OE, Sedwick WD

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Mol Pharmacol; 20(3):637-643 1981

The resistances of the methotrexate (MTX)-resistant mouse fibroblast 3T6R400 cell line to MTX and the lipid-soluble antifolate 2,4-diamino-5-(3',4'-dichlorophenyl)-6-methylpyrimidine (DDMP) were characterized and compared. Deoxyuridine incorporation was studied as a measure of drug effect iveness. The effects of these antifolates on thymidine and 32P incorporation into DNA and cell cloning efficiency were also studied. Uptake of labeled MTX was also measured in order to characterize the active transport capacity of the mutant and wild-type 3T6 cells. The inhibition of isolated dihydrofolate reductase (DHFR) by MTX and DDMP was compared in partially purified extracts from both 3T6R400 and 3T6 wild-type cells. DDMP blocked deoxyuridine, thymidine, and 32P incorporation to a greater extent than did MTX. After 24-hr exposure to MTX (less than or equal to 100 uM), no decrease in 3T6R400 cloning ability was observed; DDMP (400 uM) inhibited growth by greater than 90%. Identical slopes for the plot of initial velocity of uptake versus MTX concentration showed that the resistant cell line accumulated MTX as well as the parent cell line. DHFR of intact mutants exposed to drug for 3 hr was inhibited only 55% by 1.0 milliM MTX, where DHFR of wild-type cells was inhibited by 98%. The similar uptake rates observed in wild-type and 3T6R400 cells and the residual DHFR activity in the mutant cell line following MTX exposure suggested that a similar resistance mechanism may be involved. DDMP showed greater DHFR inhibition than MTX. The results suggested that lipid-soluble antifolates may be effective in treating cells with a pleiotropically resistant phenotype that includes transport limitations, target enzyme overproduction, and changes in target enzyme-drug affinity. (45 Refs)

52. INDUCTION OF DEOXYRIBONUCLEIC ACID DAMAGE IN HELA S3 CELLS BY CYTOTOXIC AND ANTITUMOR SESQUITERPENE LACTONES.

Woynarowski JW, Beerman TA, Konopa J
Dept. Pharmaceutical Technology and Biochemistry, Technical Univ. Gdansk, 80-952 Gdansk, Poland
Biochem Pharmacol; 30(21):3005-3007 1981

Effects of parthenolide, 1,10-epoxyparthenolide, alatolide, eupatoriopicin, vernolepin, elphantopin, and costunolide on DNA synthesis and cellular growth were tested. Incubation of HeLa S3 cells with 202 uM parthenolide resulted in an almost complete inhibition of DNA synthesis in subcellular systems derived from the cells. Addition of the cytoplasmic fraction from untreated cells did not reverse inhibition, suggesting that interference with DNA templates plays a major role. All of the lactones induced DNA damage in HeLa cells at 35 and 75x their ED50 doses. The lactones did not cause DNA breaks in isolated DNA. Results supported the theory that alkylation of DNA is a molecular basis for biological activity of sesquiterpene lactones. (16 Refs)

53. COMPARISON OF THE IV AND IP ROUTES OF ADMINISTRATION OF CISPLATIN IN DOGS.

Pretorius RG, Petrilli ES, Kean C, Ford LC, Hoeschele JD, Lagasse LD
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Cancer Treat Rep; 65(11/12):1055-1062 1981

Cisplatin at a dose of 3 mg/kg was administered to dogs either iv or ip. Cisplatin concentrations in serum, urine, and tissues were measured with a radioisotope tracer method employing 195mPt cisplatin. Systemic toxicity was monitored by serial BUN, creatinine, and wbc and platelet counts. The mode of administration did not affect systemic toxicity since the changes in renal and bone marrow functions were identical in the two groups. Serum cisplatin levels following iv administration peaked at 13.5 ug/ml at 5 min and were biphasic with rapid initial decline and a prolonged elimination phase. In contrast, levels following ip administration increased rapidly to 1.5 ug/ml at 4 hr and then decreased with the iv levels. The amount of drug recovered in the urine was similar regardless of method of administration, with approximately 50% of the injected dose excreted by Day 4. The drug levels within the tissues on Days 4 and 8 were similar, with the exception of the tissues lining the peritoneal cavity. On Day 4 the tissues lining the peritoneal cavity had 2.5-8 times higher levels of drug after ip administration, and this difference was statistically significant (p less than 0.01). Local toxic effects encountered with ip administration consisted of bloody ascites on Day 4 (4 of 9 dogs) and filmy adhesions on Day 8 (1 of 4 dogs). It is concluded that ip cisplatin chemotherapy may increase the therapeutic index for small tumors which are confined to the peritoneal cavity. (Author abstract) (28 Refs)

54. CONTINUED EXPRESSION OF VINCA ALKALOID RESISTANCE BY CCRF-CEM CELLS AFTER TREATMENT WITH TUNICAMYCIN OR PRONASE.

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Cancer Res; 42(1):184-189 1982

We have shown that a glycoprotein(s) with a mol wt of approx 180,000 exists on the surface of cultured lymphoblasts selected for resistance to vinblastine (VLB) (CEM/VLB100). The amount of this glycoprotein, which is barely detectable on the VLB-sensitive cells (CEM), appears to be related in part to the degree of resistance, up to approx 270-fold. Exposure of cells to Pronase for 45 to 60 min or growth of the cells for 2 days in tunicamycin, an inhibitor of glycoprotein synthesis, resulted in the absence of the resistance-associated glycoproteins, as determined by polyacrylamide gel electrophoresis of these treated cells after labeling the cells either with sodium [3H]borohydride or with [14C]- or [3H]glucosamine. Uptake studies with [3H]VLB revealed that CEM cells normally accumulated and retained more drug than did the CEM/VLB100 cells. While the tunicamycin or Pronase treatments slightly increased the uptake of drug by CEM cells, there was no enhanced uptake of [3H]VLB by the tunicamycin- or pronase-treated CEM/VLB100 cells, when compared with untreated controls, indicating that the loss of external surface glycoproteins did not render the resistant cells more 'leaky' to drug influx. Additionally, diminished drug retention by the CEM/VLB100 cells was unaffected by these treatments. Moreover, when CEM/VLB100 cells were grown for 2 days in the presence of tunicamycin and several concentrations of VLB, no enhanced toxicity of VLB was noted. Other experiments with [14C]glucosamine and [3H]leucine revealed that treatment with tunicamycin did not affect the distribution of proteins in these cells. Taken together, these results permit the suggestion that the carbohydrate moiety of the cell surface resistance-associated glycoproteins does not mediate resistance to the alkaloid per se; however, a role for plasma membrane proteins cannot be ruled out at this time. (Author abstract) (19 Refs)

55. CYTOKINETIC AND BIOCHEMICAL EFFECTS OF 5-IMINODAUNORUBICIN IN HUMAN COLON CARCINOMA IN CULTURE.

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Cancer Res; 42(1):117-121 1982

The semisynthetic anthracycline, 5-iminodaunorubicin (IM), was investigated to see whether modification of the benzoquinone moiety to produce a drug with low free radical potential would alter the cytotoxic and biochemical characteristics of this drug in comparison to Adriamycin (ADR), an agent with high free radical potential. Cell viability was measured in human colon carcinoma (HT-29) cells by soft-agar cloning. Upon exposure of either log-phase or early plateau-phase cells for 2 hr to IM or ADR, a threshold exponential cell lethality curve was obtained. Prolonging drug exposure to 24 hr produced an exponential decline in cell survival and a marked reduction in viability of both log-phase and early plateau-phase cells. Inhibition of DNA synthesis in log-phase cells after 2 and 24 hr of exposure to IM and ADR paralleled the increased cell lethality produced by the drugs. In contrast, total RNA synthesis was not inhibited by IM, whereas ADR impaired both RNA and DNA synthesis. Nuclear rRNA synthesis was not significantly inhibited following 24 hr of exposure to 10(-7) M ADR or IM but was inhibited by 85 and 35% at 10(-6) M ADR or IM, respectively. The affinity of IM and ADR for HT-29 DNA was measured in vitro by displacement of acridine orange binding and was found to be similar for both analogs. These studies suggest that the cytotoxicity of IM and ADR results from the interactions of these drugs with DNA. (Author abstract) (20 Refs)

56. EFFECTS OF TUNICAMYCIN ON ANTHRACYCLINE RESISTANCE IN P388 MURINE LEUKEMIA CELLS.

Chou TH, Kessel D
(c/o Kessel) Dept. Oncology, Wayne State Univ. Sch. Medicine, 3990 John R., Detroit, MI, 48201
Biochem Pharmacol; 30(22):3134-3136 1981

The inhibition of glycoprotein synthesis in an adriamycin (ADR)-resistant subline of P388 murine leukemia (P388/ADR) was studied for its effects on anthracycline responsiveness and drug efflux. Labeled daunorubicin (DR), cross resistant with P388/ADR in vivo, was used. Cell surface effects of tunicamycin (TC) were independently monitored by a two-phase partitioning method. TC inhibited fucose incorporation indicative of glycoprotein synthesis by 60%. TC increased the partition coefficient of both P388 and P388/ADR cells before and after neuraminidase treatment. Partitioning behavior was primarily affected by degree of membrane sialation, not by TC binding to cell surface. TC did not affect the capacity of P388 and P388/ADR cells for concentrative uptake of cycloleucine, a non-metabolized amino acid. P388 and P388/ADR viability was decreased by approx 50% following 1 hr exposure to 0.04 ug/ml and 0.060 ug/ml DR, respectively. TC (3 ug/ml) inhibited P388 and P388/ADR cell growth for 24 hr; after that time normal growth resumed. Exposure of TC-treated cells to DR had no effect on these results. Impaired DR accumulation, correctable by the addition of 10 milliM azide and deletion of glucose from the medium, was observed in P388/ADR cells. DR accumulation or efflux was not affected by prior exposure of either cell line to TC. Suppression of glycoprotein synthesis altered cell surface properties but had no effect on DR transport characteristics or drug responsiveness. Enhanced glycosylation of cell surface components was associated with development of drug resistance patterns in P388/ADR, but was not a determinant of such resistance. (25 Refs)

57. WHY DO COLON TUMORS RESPOND POORLY TO CHEMOTHERAPEUTIC AGENTS?

van Putten LM, Sluijter EA, Smink T, Mulder JH
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Recent Results Cancer Res; 79:10-18 1981

Possible causes of poor response by colonic tumors to chemotherapy are reviewed. Six factors are discussed: (1) tumor cells may be relatively insensitive to chemotherapeutic agents (CA), (2) different tumors of a given type may possess different sensitivities to CA, (3) since proliferating cells respond better to CA, insensitivity may indicate a low rate of proliferation, (4) exposure of tumor cells to CA may be limited by poor tumor vascularization, (5) a drug-resistant cell line or lines may emerge soon after exposure to each CA (resistance would depend on the spontaneous mutation rate and the number of cells in the tumor cell population), and (6) surviving tumor cells may proliferate rapidly due to improved nutritional and crowding factors. Current data do not permit a definite conclusion about colonic tumors. Factors 1, 2, and 5 may be analyzed by studying cellular properties. Factor 3 does not appear relevant. Factor 4 could be verified by pharmacokinetic studies and factor 6 by cell kinetic studies. Poor tumor response to chemotherapy is probably the result of a combination of factors. (15 Refs)

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CANCERGRAM

ANTITUMOR AND ANTIVIRAL AGENTS

Experimental Therapeutics, Toxicology, Pharmacology

MAY, 1982

SERIES CB20 No. 82/05

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ANTITUMOR AGENT EFFICACY IN VIVO

1. EFFECT OF LIPOSOME-ENTRAPPED 5-FLUOROURACIL ON EHRLICH ASCITES TUMOUR BEARING MICE.

Mazumder A
Indian Inst. Experimental Medicine, Calcutta 700 032, India
Indian J Biochem Biophys; 18(2):120-123 1981

Effects of free and liposome-entrapped 5-fluorouracil (5-FU) on tumor regression were compared in groups of 20 male

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Swiss mice bearing Ehrlich ascites tumors. Packed cell vol (PCV) of ascites fluid decreased as the dose of free 5-FU increased; tumor regression was most pronounced at 500 ug (per mouse); survival 15 days after transplantation was 22% compared to 4% in controls. PCV decreased at a higher rate after administration of liposome-entrapped 5-FU (90-270 ug) than after administration of free drug (90 ug), and the concentration of entrapped drug required for tumor regression appeared to be much less than that of free drug. PCV was lower following iv injection of 270 ug of liposome-entrapped 5-FU than after ip injection of the same dose (0.5 vs 0.9). Survivals were 20 and 22%, respectively, after iv and ip injection. (10 Refs)

2. CHEMOTHERAPY OF ASCITES HEPATOMA CELL TRANSPLANTATION-INDUCED RAT BRAIN TUMOR MODEL - EFFECTS OF ACNU AND ADRIAMYCIN AND THEIR TISSUE CONCENTRATIONS.

Kida Y, Kobayashi T, Yoshida J, Shibuya N, Kageyama N
Dept. Neurosurgery, Nagoya Univ., Nagoya 466, Japan
Neurol Med Chir (Tokyo); 21(8):839-846 1981

Effects of aminochloroethyl nitrosourea (ACNU) and adriamycin (ADR) were studied in a rat brain tumor model. Brain tumors were induced by percutaneous intracerebral inoculation of ascites hepatoma cells (AH-7974) via a suborbital route through an optic canal. ACNU was administered to five groups of rats (controls, 10 mg/kg day 1 after inoculation, 10 mg/kg day 4, 1 mg/kg day 7, or 10 mg/kg days 4 and 7), and ADR was administered to five groups of rats (controls, 1 mg/kg day 4 after inoculation, 5 mg/kg day 4, 5 mg/kg day 7, or 5 mg/kg days 4 and 7). AH-7974 cell growth was inhibited markedly in vitro by 10 and 20 ug/ml of ACNU and by 2.5 ug/ml of ADR 2 days after treatment. Compared to control rats which had median survival of 12.5 days after inoculation, rats administered ACNU, especially on day 4, had increased life spans (median survival greater than 30 days). Compared to control rats, life spans of rats given ADR was not significantly prolonged. However, rats given ADR on day 7 had slightly prolonged life span, and although the rats given the ADR on both day 4 and 7 had a markedly shorter life span, autopsy showed marked shrinkage or disappearance of the brain tumors. That is, as the lethal dose was approached, effects were observable. Both drugs were effective against sc transplanted AH-7974 tumors. ACNU and ADR were thought to be dose- and time-dependent, respectively, in their effects. (23 Refs) (In JPN)

3. CYTOKINETIC BEHAVIOR OF EHRLICH ASCITES TUMOR AFTER IN VIVO TREATMENT WITH CIS-DIAMMINEDICHLOROPLATINUM(II) AND METALLOCENE DICHLORIDES.

Kopf-Maier P, Wagner W, Liss E
Institut fur Anatomie, Freine Universitat Berlin, Konigin-Luise-Strasse 15, D-1000 Berlin 33, W. Germany
J Cancer Res Clin Oncol; 102(1):21-30 1981

The influence of an in vivo treatment with optimally tumor-inhibiting doses of cis-diamminedichloroplatinum(II) (DDP), titanocene dichloride (TDC), and vanadocene dichloride (VDC) on the DNA distribution pattern, determined by pulse-cytophotometry, and on the mitotic activity of EAT cells is investigated. Whereas DDP causes an immediate and long-lasting decrease of mitoses but no disturbances of the EAT cell kinetics, a marked G2 block with a maximum at 10-12 hr a t and an irreversible and extensive mitotic depression is evoked by TDC. In the case of DDP and TDC, the tumor cells are removed several days a t by cells belonging to the defensive system of the host animals. In contrast, VDC induces partially synchronized waves after a transient suppression of mitoses and reversible cell accumulation in the late S and in the G2 phases. Additionally, 5-16% of the cells become polyploid after VDC treatment. (Author abstract) (17 Refs)

4. THE MECHANISM OF ACTION OF 1-(2-CHLOROETHYL)-3-(METHYL ALPHA-D-GLUCOPYRANOSE-6-YL)-1-NITROSOUREA (MCNU) IN CULTURED HELA S3 CELLS.

Kanamaru R, Sato H, Asamura M, Kakuta H, Wakui A
Dept. Clinical Cancer Chemotherapy, Res. Inst. for Tuberculosis and Cancer, Tohoku Univ., Sendai-shi, Miyagi Pref. 980, Japan
Gan To Kagaku Ryoho; 8(6):877-884 1981

The mechanism of action of 1-(2-chloroethyl)-3-(methyl alpha-D-glucopyranose-6-yl)-1-nitrosourea (MCNU) was studied in cultured HeLa S3 cells. The colony formation of the cells, as an index of proliferative ability, was inhibited completely by treatment with MCNU at 200 ug/ml for 60 min and the drug concentration required for 50% inhibition was 40 ug/ml. When the cells were incubated with [^{14}C-ethylene]-MCNU, the radioactivity bound to the acid-insoluble fraction increased linearly up to 24 hr. In contrast, when the cells were incubated with [14C-glucose]MCNU, almost no radioactivity was detected throughout the incubation period up to 24 hr, suggesting that MCNU possesses strong alkylating activity and rather weak carbamoyling activity. RNA and protein synthesis were more strongly suppressed than DNA synthesis. At 100 ug/ml and 200 ug/ml, DNA synthesis was inhibited by 75% and 90%, and RNA synthesis was inhibited by 17% and 20%, respectively, after 24 hr. Single-strand scission of DNA was observed 24 hr after treatment with 100 ug/ml for 60 min. Although marked unscheduled DNA synthesis was induced at this time, no rejoining of the damaged DNA strands occurred even after 48 hr, indicating that the last step of the DNA repair process, ligation of the nicked strand, was inhibited by the drug. Furthermore, MCNU was found to have an inhibitory effect on the processing of ribosomal RNA. (13 Refs) (In JPN)

ANTITUMOR AGENT EFFICACY IN VITRO

5. LOCAL CHANGES OF DNA STRUCTURE INDUCED BY N-METHYL-N-NITROSOUREA.

Krugliakova KE, Zhizhina GP, Smotriaeva MA
Inst. Chemical Physics, Moscow, USSR
Stud Biophys; 85(1):11-12 1981

N-methyl-N-nitrosourea (MNU) was shown to modify the structure of DNA molecule. MNU induced double-stranded and single-stranded breaks, thermolabile sites, and alkali-labile sites. The av size of MNU-induced DNA damage was 30 bases. (4 Refs) (In RUS)

6. INFLUENCE OF DURATION OF EXPOSURE TO 5-FLUOROURACIL ON ANTIPROLIFERATING ACTIVITY AGAINST CULTURED MURINE LYMPHOMA CELLS.

Kanzawa F, Hoshi A, Kuretani K

Pharmacology Div., Natl. Cancer Center Res. Inst., 1-1 Tsukiji 5-chome, Chuo-ku, Tokyo, 104, Japan

Br J Cancer; 44(5):757-759 1981

Effects of exposure time on the cytotoxicities of 5-fluorouracil (FU), fluorouridine (FUR), and 5-fluoro-2'-deoxyuridine (FUdR) in murine lymphoma L5178Y cells were compared to analyze the mechanism of FU cytotoxicity. Proliferation ratios of L5178 cells exposed to varying concentrations of FU for 1, 3, 6, 12, 18, and 24 hr were determined. After a 1-hr exposure to FU (5 uM or less), L5178Y cells grew continuously. At FU concentrations of 10, 15, 20, 30, and 50 uM, cell proliferation was inhibited by 89.20, 97.35, 99.23, 99.53, and 99.64%, respectively; the IC99 (drug concentration inhibiting cell proliferation by 99%) of FU was 19 uM. The antitumor activity of FU increased with exposure time; IC99 values for FU exposures of 3, 6, and 12 hr were 8.5, 3.6, and 0.98 uM, respectively. After FU exposures of greater than 12 hr, no increase in antitumor activity was observed. The time-dependent response curve of FU was similar to that of FUR but differed greatly from that of FUdR. One hr exposure to FUdR (2.5 uM) inhibited cell proliferation by 99%; the FUdR dosage required for inhibition after a 1-hr exposure was approx 1,000x greater than than that required after a 24-hr exposure. The IC99 value for FUR (0.16 uM) after a 1-hr exposure was only 6.7x that obtained after a 24-hr exposure. The results suggested that interference with RNA function may be important in the cytotoxicity of FU and FUR and that inhibition of DNA synthesis via activation of thymidylate synthetase may be important in FUdR cytotoxicity. (14 Refs)

7. ADRIAMYCIN DAMAGE: IN VIVO REPAIR BY LYMPHOMA CELLS.

Potmesil M, Levin M, Goldfeder A, Silber R

Dept. Radiology and New York Univ. Cancer Center, New York Univ. Medical Sch., 550 First Ave., New York, NY, 10016

JNCI; 67(6):1259-1263 1981

The in vivo repair of ADR-induced cell damage was investigated in the DBA3 transplantable mouse lymphoma. After a single injection of 5 or 15 mg ADR/kg body wt into DBA/2J mice, the survival fraction of clonogens showed a 2.2-to 4.4-fold decrease at 12 or 18 hr post injection and returned to pretreatment levels within 6 hr. These changes were accompanied by the appearance and disappearance of DNA crosslinks and breaks. Because cell division and/or cell loss could not explain the return of clonogens to pretreatment level, the results strongly suggested repair of ADR damage in tumor cells in situ. Such an efficient repair mechanism, responding to a high toxic dose of ADR, constitutes a therapeutically unfavorabl e event that may contribute to drug resistance. (Author abstract) (27 Refs)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

8. SPECIFIC INHIBITION OF THE SUBUNITS OF RIBONUCLEOTIDE REDUCTASE AS A NEW APPROACH TO COMBINATION CHEMOTHERAPY.

Cory JG, Sato A, Lasater L

Dept. Biochemistry, Univ. South Florida Coll. Medicine, Tampa, FL, 33612

Adv Enzyme Regul; 19:139-150 1981

The activity of ribonucleotide reductase can be inhibited by agents such as hydroxyurea, guanazole, IMPY, MAIQ, IQ, Inox, 5'-deoxyinox and various deoxyribonucleoside triphosphates. Since the reductase from mammalian cells could be separated into its non-identical components (non-heme iron subunit and effector binding subunits), it was possible to show that these inhibitors are specifically directed toward only one of the subunits. It was shown that the inhibition of reductase by hydroxyurea, guanazole and IMPY was potentiated by the iron-chelating agents EDTA, Desferal and 8-hydroxyquinoline while the inhibition by MAIQ and IQ was reversed by the iron-chelating agents. Combinations of reductase inhibitors such as IMPY/dGTP, IMPY/Inox and hydroxyurea/dATP gave synergistic inhibition while combinations of MAIQ/IMPY and IMPY/hydroxyurea caused antagonistic effects. However, it was not possible to predict a priori which combinations would lead to the anticipated results. (Author abstract) (28 Refs)

9. EFFECT OF ULTRASOUND-INDUCED HYPERTHERMIA AND CIS-DIAMMINEDICHLORIDE PLATINUM II ON MURINE RENAL FUNCTION.

Elkon D, Lacher DA, Rinehart L, Wills MR, Savory J, Constable WC, Baker DG

Div. Radiation Oncology, Univ. Virginia Medical Center, Box 383, Charlottesville, VA, 22908

Cancer; 49(1):25-29 1982

Murine renal function was evaluated after ultrasound-induced kidney hyperthermia (42.5 C and 46.5 C for 35 min) and the administration of cis-diamminedichloride platinum II (8 mg/kg). A quantitative immunonephelometric technique was employed to determine urinary total protein (TP) and albumin (Alb) 1-180 days post-treatment. Hyperthermia of 46.5 C elevated urinary TP excretion significantly more than that of 42.5 C cis-diamminedichloride platinum (Cis DDP) administration greatly increased urine TP with a peak mean TP concentration of 488 ug/ml, 4 days after Cis DDP (normal range was 26-48 ug/ml). This returned to normal by day 14. The TP excretion after 42.5 C hyperthermia with concurrent Cis DDP was similar to Cis DDP alone, implying there was no potentiation of early or late Cis-DDP-induced renal damage by hyperthermia. Late mouse mortality was greater ($p = 0.08$) after Cis DDP alone, than Cis DDP with 42.5 C hyperthermia. There was a statistically significant increase (p less than 0.05) in the Alb/TP excretion ratio after the addition of 42.5 C hyperthermia to Cis DDP, implying an alteration in the site or nature of the Cis DDP renal lesion by hyperthermia. (Author abstract) (32 Refs)

10. CHEMOTHERAPY OF L1210 LEUKEMIA WITH 5-AZACYTIDINE IN COMBINATION WITH VINCRISTINE, ADRIAMYCIN, OR BETA-CYTOSINE ARABINOSIDE.

Present CA, Vietti TJ, Valeriote F, Coulter DM
Dept. Medical Oncology, City Hope Natl. Medical Center, 1500 East Duarte Rd., Duarte, CA, 91010
JNCI; 67(6):1283-1288 1981

The cytotoxicity of vincristine (VCR), beta-cytosine arabinoside (Ara-C), or adriamycin (ADRIA) in combination with 5-azacytidine (Aza-CR) to L1210 leukemia in vivo was measured to determine if schedule-dependent synergistic or antagonistic drug interaction occurred. Two dose levels of Aza-CR were studied (0.1 and 0.5 mg/mouse), and cytotoxicity was measured by the spleen colony assay. For the combination of Aza-CR plus VCR, cytotoxicity was essentially additive or antagonistic when VCR preceded Aza-CR and additive or synergistic when VCR followed Aza-CR. When Aza-CR was combined simultaneously with either Ara-C or ADRIA, cytotoxicity was markedly antagonistic but was additive if drugs were given sequentially. When Ara-C was given as a 24-hr infusion before Aza-CR, the resultant cell kill was antagonistic (although slightly greater than that obtained for Ara-C alone). However, antagonism was even more marked when Aza-CR was given before the 24-hr infusion of Ara-C; cell kill was less than that observed with Ara-C alone. Synergistic cytotoxicity was observed only with VCR administered after a low dose of Aza-CR. Therefore, scheduling of drugs in combination with Aza-CR may be critical in the determination of the antileukemic cytotoxic effects. (Author abstract) (18 Refs)

11. MODIFICATION OF THE ORAL RADIATION DEATH SYNDROME WITH COMBINED WR-2721 AND MISONIDAZOLE.

Grigsby P, Maruyama Y
Radiation Medicine Dept., Univ. Kentucky Medical Sch., Lexington, KY, 40536
Br J Radiol; 54(647):969-972 1981

In order to investigate the combined use of radioprotective and radiosensitizing chemicals we have used WR-2721 and misonidazole to study their combined chemical toxicity and radiomodifying effects in our model using the oral radiation death (ORD) syndrome as the endpoint. Our data demonstrate that WR-2721 does protect against the ORD syndrome. Misonidazole does not sensitize the normal oral cavity to local irradiation. WR-2721 and misonidazole produce additive toxicity when injected simultaneously and the combination can provide an overall protective response to the ORD syndrome. We conclude that the combination may be potentially useful for the treatment of cancers of the oral cavity. (Author abstract) (12 Refs)

12. HYPERTHERMIC THERAPY OF BLADDER CANCER. II. KINETICS OF CELL KILLING BY HYPERTHERMIA PLUS BLEOMYCIN.

Kubota Y
Dept. Urology, Yokohama City Univ. Sch. Medicine, Yokohama, Japan
Nippon Hinyokika Gakkai Zasshi; 72(6):735-741 1981

Kinetics of cell killing with hyperthermia and mechanism of synergistic cytotoxicity due to a combination of hyperthermia and bleomycin (BLM) were studied in HeLa cells. The HeLa cells were cultured in Eagle minimum essential medium with 10% fetal calf serum, penicillin, and streptomycin. Compared to control cells, the hyperthermia-treated (43 C for 45 min) cell colonies showed almost no growth up to day 2 after hyperthermia; thereafter, to day 5, the treated cells were divided into two groups - those that had inhibited mitosis and those that showed recovery of mitosis. Compared to sedimentation profiles, which were determined with the aid of alkaline sucrose gradient analysis, of cell-DNA from untreated (37 C for 1 hr) HeLa cells, those of HeLa cells treated with 43 C or 45 C hyperthermia for 1 hr had lower main peaks (indicating lower percentage recovered radioactivity), but the position of the peaks were the same as in the controls. Combination of hyperthermia and BLM inhibited the recovery of growth capacity in the group of cells that showed recovery of mitosis when treated with hyperthermia alone. Combination of hyperthermia and BLM also produced more DNA single-strand breaks than BLM treatment alone and inhibited the repair of DNA single-strand breaks due to BLM. No synergistic inhibition of the HeLa cells' synthesis of DNA, RNA, or protein was observed with the combination of hyperthermia and BLM. (23 Refs) (In JPN)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

13. STUDIES ON THE TOXICITY OF CHLORINATED P-NITROBIPHENYL ETHER. I - METHEMOGLOBIN FORMATION IN VITRO AND IN VIVO INDUCED BY NITROSO AND AMINO DERIVATIVES OF CHLORINATED BIPHENYL ETHER.

Miyauchi M, Koizumi M, Uematsu T
(c/o Uematsu) Dept. Chemical Hygiene, Hokkaido Inst. Pharmaceutical Sciences, Otaru 047-02, Japan
Biochem Pharmacol; 30(24):3341-3346 1981

Methemoglobin (Mg) formation by nitroso and amino derivatives of chlorinated biphenyl ether was investigated. The nitroso derivatives used induced Mg formation in suspensions of human RBC. Ability to induce Mg formation among the nitroso derivatives was the highest for nitrosobenzene, followed by p-nitrosobiphenyl ether, 4-chloro p-nitrosobiphenyl ether, 2,4-dichloro p-nitrosobiphenyl ether and then 2,4,6-trichloro p-nitrosobiphenyl ether. Therefore, the ability to induce Mg formation depended on the number of chlorines rather than on the position of chlorine substitution on the phenoxy group in the molecule. Since lactate decreased but glucose and xylitol increased the Mg level produced by the nitroso compounds, this reaction would appear to require an NADPH-dependent enzyme system in RBC. The amino derivatives used induced Mg formation in suspensions of human RBC with rat liver homogenates. Ability to induce methemoglobin formation among the amino derivatives was the highest for p-aminobiphenyl ether, followed by 4-chloro p-aminobiphenyl ether, 2,4-dichloro p-aminobiphenyl ether, 2,4,6-trichloro p-aminobiphenyl ether, and then aniline. After ip injection, methemoglobinemia was induced by p-aminobiphenyl ether, aniline, and 2,4-dichloro p-aminobiphenyl ether but not by 2,4,6-trichloro p-aminobiphenyl ether over the period tested. The order of Mg formation was p-aminobiphenyl ether greater than or equal to 4-chloro p-aminobiphenyl ether greater than aniline greater than or equal to 2,4-dichloro p-aminobiphenyl ether. Oral administration gave almost the same result as ip injection. The max Mg levels produced by the amino derivatives were highest for 4-chloro p-aminobiphenyl ether, followed by p-aminobiphenyl ether, 2,4-dichloro p-aminobiphenyl ether, aniline, and then

2,4,6-trichloro p-aminobiphenyl ether. However, the Mg level produced by 2,4,6-trichloro p-aminobiphenyl ether was very low and not significantly greater than the background level. (Author abstract) (35 Refs)

14. EFFECT OF MALNUTRITION ON METHOTREXATE TOXICITY AND TISSUE LEVELS OF DIHYDROFOLATE REDUCTASE IN THE RAT.

Grossie VB, Ho DH, Loo TL
Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer Treat Rep; 66(1):85-89 1982

The effect of malnutrition on the toxicity of methotrexate (MTX) and the dihydrofolate reductase (DHFR) content of the liver, small intestinal mucosa, kidney, and bone marrow of male Sprague-Dawley rats was studied. Malnutrition was induced by reducing the daily intake of chow to one third for 14 days. A single ip treatment with MTX was lethal to three of nine rats at a dose of 37.5 mg/kg and to three of five rats at a dose of 50.0 mg/kg but caused only transient wt loss to similarly treated full-fed, age-matched controls. Although the body weights and absolute tissue weights were reduced in malnourished rats, only the liver and small intestinal mucosa were smaller relative to their respective body weights. The cellular DHFR content of liver and bone marrow from malnourished rats was lower than that from the controls, although in terms of the content per gram of tissue, there was no significant change. While the total DHFR in malnourished rat tissues was significantly lower than that for the controls, only the total-liver DHFR was lower relative to the body wt. The increased toxicity of MTX to malnourished rats may be related to the DHFR levels in the liver and bone marrow. (Author abstract) (15 Refs)

15. METABOLIC ACTIVATION AND CYTOTOXICITY OF CYCLOPHOSPHAMIDE IN PRIMARY CULTURES OF POSTNATAL RAT HEPATOCYTES.

Acosta D, Mitchell DB
Dept. Pharmacology, Coll. Pharmacy, Univ. Texas at Austin, Austin, TX, 78712
Biochem Pharmacol; 30(23):3225-3230 1981

We have developed a model of primary cultures of postnatal rat hepatocytes to characterize the metabolic activation of xenobiotics to toxic intermediates and to study the mechanism(s) by which these chemicals produce cellular injury. This model was employed to investigate the cytochrome P-450 mediated biotransformation of cyclophosphamide (CP) to cytotoxic metabolites that nonspecifically alkylate DNA and cellular proteins. The parenchymal cells were isolated by an in situ collagenase perfusion technique and cultured for 24 hr prior to drug treatment. The cultures were then exposed to CP concentrations ranging from 1 x 10(-4) M to 1 x 10(-3) M for 24 hr. Initial studies indicated minimal toxicity to non-replicating parenchymal hepatocytes maintained in ornithine-supplemented, arginine-deficient medium. The addition of arginine permitted the overgrowth of fibroblasts in the same culture system. These fibroblasts then became the target of alkylating CP metabolites produced by the parenchymal cells. By day 3 after CP administration, cell number and total protein per dish decreased by over 40%. The morphology of the cultures changed dramatically because of fibroblast destruction. The cytotoxicity to dividing fibroblasts was eliminated by administering 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride (SKF 525-A), an inhibitor of the cytochrome P-450 monooxygenase system, to the co-cultures treated with CP. The alkylating metabolites of CP produced by parenchymal cells and released into the culture medium were quantitated by reacting aliquots of medium from CP-treated cells with 4-(p-nitrobenzyl)pyridine. These results provide both direct and indirect evidence of drug metabolism in cultured cells and suggest that this co-culture system can be utilized to evaluate the metabolic activation of xenobiotics. (Author abstract) (49 Refs)

16. DIMINISHED TOXICITY OF METHOTREXATE IN CD2F1 MICE PRETREATED WITH CYCLOHEXIMIDE.

Panasci L, Polizzi G, Palmer S
Oncology Center, Lady Davis Inst. Medical Res., Jewish General Hosp., Montreal, Quebec, H3T 1E2, Canada
Cancer Lett; 15(1):81-86 1982

The prevention of lethal toxicity of methotrexate in mice by prior cycloheximide administration is described. The therapeutic index of methotrexate was not increased. The lethal toxicity of single doses of cycloheximide or methotrexate was determined in normal CD2F1 mice. The lethal toxicity of methotrexate administered 1, 3, or 6 hr after cycloheximide was also determined in CD2F1 mice. The murine P388 leukemia was utilized to determine antitumor activity. Treatment was administered 1 day after the ip implantation of two million P388 leukemia cells. The percentage of increased life span (ILS) was calculated from the survival of control tumor-bearing mice that received a similar volume of 0.9% NaCl. Cycloheximide at 100 mg/kg administered ip to P388 tumor-bearing CD2F1 mice diminished protein synthesis in the liver, spleen, kidneys, lungs, small intestine, and P388 tumor 75 min after administration. Six hours after administration of cycloheximide, recovery of protein synthesis was complete in all tissues except the tumor and bone marrow. Recovery of protein synthesis in the jejunum was complete at 3-hr. Protein synthesis suppression was still present in the tumor 9 hr after administration of cycloheximide. Single ip injections of methotrexate at 60 mg/kg produced lethal toxicity in 10% of the normal CD2F1 mice, 100 mg/kg in 30%, and 150 mg/kg in 60%. The administration of cycloheximide prior to methotrexate diminished the lethal toxicity of methotrexate even 6 hr after cycloheximide administration. While cycloheximide diminished the lethal toxicity of methotrexate 150 mg/kg to that equivalent to methotrexate 60 mg/kg alone, the sequential administration of these drugs only resulted in an ILS of approx 20%. (7 Refs)

17. COLLAGEN LYSYL OXIDASE ACTIVITY IN THE LUNG INCREASES DURING BLEOMYCIN-INDUCED LUNG FIBROSIS.

Counts DF, Evans JN, Dipetrillo TA, Sterling KM, Kelley J
Dept. Biochemistry, Univ. Vermont, Given Building, Burlington, VT, 05405
J Pharmacol Exp Ther; 219(3):675-678 1981

Increased lysyl oxidase activity was seen in the lungs rats observed for to 322 days after intratracheal instillation of bleomycin (640 ug/165 g of body wt in 0.5 ml of sterile saline). This increase preceded the high accumulation of hydroxyproline and desmosine. Lysyl oxidase may be an important enzyme with regard to development of pulmonary fibrosis. (22 Refs)

18. ASSESSMENT OF BLEOMYCIN-, TALLYSOMYCIN-, AND POLYAMINE-MEDIATED ACUTE LUNG TOXICITY BY PULMONARY LAVAGE ANGIOTENSIN-CONVERTING ENZYME ACTIVITY.

Newman RA, Hacker MP, Kimberly PJ, Braddock JM

Dept. Pharmacology, Coll. Medicine, Univ. Vermont, Burlington, VT, 05405

Toxicol Appl Pharmacol; 61(3):469-474 1981

The relative capacities of bleomycin (BLM) and related tallysomycins (TLM) to cause pulmonary endothelial cell damage were investigated. Single intrathecal injections of BLM (3.5 mg/kg), TLM (0.86-2.1 mg/kg), putrescine (PUT) (0.6 mg/kg), or spermidine (SPD) (0.12 mg/kg) were administered to one group of rats; another group received injections of putrescine or hirudonine (HDN) 18 and 3 hr prior to BLM. Pulmonary endothelial cell damage was assessed by lavage and serum angiotensin-converting enzyme (ACE) activity within 7 days of injection. Single equitherapeutic doses of BLM and TLM produced similar dose related increases in the pulmonary lavage content of ACE activity. Each of the TLM drugs showed potential to cause acute pulmonary toxicity; no TLM was less actively pneumotoxic than BLM. Serum ACE activity rose to 112% of control levels in BLM treated rats and to 118%, 100%, and 82% of control levels in TLM A, TLM B, and TLM S10B treated rats, respectively. None of the changes in serum ACE activity were significant. Intratracheal administration of PUT or SPD produced epithelial cell metaplasia, interstitial edema, and fibrosis 4 wk after treatment. Pretreatment with HDN or PUT alone resulted in a reduction of ACE in lavage fluid, although neither polyamine altered the BLM-mediated increase in pulmonary lavage ACE content. Various TLM drugs apparently produce acute pulmonary injury despite specific structural differences from BLM. (19 Refs)

19. LOCAL AND SYSTEMIC TOXICITY RESULTING FROM LARGE-VOLUME IP ADMINISTRATION OF DOXORUBICIN IN THE RAT.

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Cancer Treat Rep; 66(1):157-161 1982

Doxorubicin was administered to rats in a simulated 'belly bath' protocol. Fifty milliliters of various concentrations of drug solution was administered ip and was allowed to remain in situ for either 4 or 36 hr prior to removal. Animals were analyzed at 2, 14, and 60 days after treatment. Doses ranged from lethal (75 and 150 ug/ml for 4 hr; 12 and 24 ug/ml for 36 hr) to nontoxic (5 ug/ml for 4 hr). The most common lesion in surviving animals was chronic fibrosing peritonitis. Grossly, there were large volumes of peritoneal fluid in animals exposed to low concentrations (12 and 24 ug/ml) for 36 hr, but peritoneal adhesions were the most commonly observed finding when higher concentrations (20-150 ug/ml) were used for 4 hr. Commonly observed systemic toxic effects (bone marrow, gastrointestinal tract, and heart) were not seen in this study. Vehicle-treated control animals were negative for all histologic lesions and gross observations. (Author abstract) (16 Refs)

20. REDUCED TOXICITY OF DAUNORUBICIN BY CONJUGATION TO DEXTRAN.

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Cancer Treat Rep; 66(1):107-114 1982

The Daunorubicin-dextran conjugate (dau-dex) was compared to free daunorubicin for acute and subacute toxicity and efficacy in tumor chemotherapy. LD50 and LD2 values of dau-dex are about threefold higher than those of the free drug. The therapeutic index of dau-dex is also higher, manifesting a 'safe-region' in which no mortality occurs either from YAC lymphoma or from drug toxicity. Dau-dex caused almost no damage to heart tissue during the 2 mo following four injections of the therapeutic dose and caused no change in the differential count of bone marrow cells. Altogether, the subacute toxicity of dau-dex is much lower than that of free daunorubicin, as expressed by negligible histologic damage to all organs examined and compared to the massive atrophy of spleen and bone marrow effected by the free drug. (Author abstract) (12 Refs)

21. VINBLASTINE AND CYTOCHALASIN B EFFECTS ON DISTRIBUTION OF CONCANAVALIN A RECEPTORS IN NORMAL ATTACHED 3T3 CELLS.

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Cell Mol Biol; 27(4):333-339 1981

The effect of the antimicrotubule drug, vinblastine (VB), and of the antimicrofilament drug, cytochalasin B (CB), on the surface distribution of concanavalin A (ConA) binding sites was investigated on normal attached 3T3 cells. When labeled with ferritin-conjugated concanavalin A (Fer-ConA) or with ConA followed by horseradish peroxidase (ConA-HRP), normal 3T3 cells showed a slightly clustered distribution of ConA binding sites. These clusters were distributed randomly over the whole cell surface. This distribution of ConA-receptor complexes was not altered by treatment of cells with CB, despite the marked changes that this drug produced in cell morphology. On the other hand, treatment of 3T3 cells with VB produced marked changes, not only cell morphology, but also in the organization of ConA binding sites: ConA-receptor complexes were cleared from peripheral areas and moved towards the perinuclear part of the cell. The redistribution of ConA receptors is not dependent on VB treatment only, but also needs ConA binding, because in cells treated with VB and fixed before labeling with ConA, the redistribution does not occur. These results are discussed in relation with the role played by microtubules and microfilaments in redistribution of ConA binding sites. (Author abstract) (17 Refs)

22. EFFECT OF BUSULFAN ON THE GERM CELL LINE OF THE QUAIL EMBRYO.

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Arch Anat Microsc Morphol Exp; 70(4):251-258 1981

The effect of busulfan (3.8 and 9.6 mg/kg), injected into the albumen of quail eggs at hr 56 of incubation, on the germ cell lines of male and female quail embryos was studied. The survival rates, determined on day 15 of incubation, were 9/24 for the lower dose and 7.24 for the higher dose vs 6/10 for the untreated controls. The corresponding hatching rates were 5/

24, 3/24 and 4/10. None of the 24 surviving embryos examined had external developmental anomalies. On day 15 of incubation the female embryos treated with the lower dose of busulfan were fertile and had ovarian primordium similar to those in the controls, but total absence of typical germ cells was seen in the embryos treated with the higher dose. Signs of gonocyte degeneration and considerable reduction of the thickness of the ovarian cortex were seen in the latter group on day 15 of incubation and 2 days after hatching. In the male embryos, 3/4 testes were sterile on day 15 of incubation. The testes were usually of reduced size due to a reduction of the number and size of the testicular cords. (19 Refs) (In FRE)

23. THE EFFECTS OF ADRIAMYCIN IN VITRO AND IN VIVO ON HEPATIC MICROSOMAL DRUG-METABOLIZING ENZYMES: ROLE OF MICROSOMAL LIPID PEROXIDATION.

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Toxicol Appl Pharmacol; 61(3):313-325 1981

The role of lipid peroxidation in the effects of adriamycin both in vitro and in vivo on microsomal cytochrome P-450, NADPH-cytochrome-c reductase, aminopyrine N-demethylase, UDP-glucuronyltransferase, and glucose-6-phosphatase activities was investigated. Male rats received 10 or 15 mg/kg of adriamycin ip 12, 24, or 48 hr prior to sacrifice; a separate group received 5 mg/kg of adriamycin ip 7, 4, and 1 day before sacrifice. Liver microsomes were then assayed for lipid peroxidation and cytochrome P-450; incubations to determine drug metabolizing enzyme activities were immediately conducted. Liver microsomes incubated with the NADPH generating system showed a 6x increase in lipid peroxidation. Microsomes preincubated with adriamycin and EDTA in the absence of the NADPH generating system showed a 35% decrease in cytochrome P-450 concentration and in aminopyrine activity. Both control NADPH- mediated and NADPH-dependent adriamycin-stimulated microsomal peroxidation reduced cytochrome P-450 content 85%, and inhibited aminopyrine demethylation 70%. UDP-glucuronyltransferase activity was increased nearly 5x by adriamycin-stimulated peroxidation; glucose-6-phosphatase activity was nearly abolished by lipid peroxidation. While acute adriamycin treatment had no significant effect on hepatic microsomal drug metabolizing enzymes, subacute injections appreciably depressed the activity. Lipid peroxidation was significantly increased after subacute injections. No change was observed in glucose-6-phosphatase or UDP-glucuronyltransferase activities. Adriamycin was apparently capable of impairing hepatic drug metabolism by stimulating membrane lipid peroxidation; the mechanism by which in vivo treatment decreased the activity of the drug mono-oxygenase system remains unclear. (53 Refs)

PHARMACOKINETICS OF ANTITUMOR AGENTS

24. NONLINEAR PHARMACOKINETICS OF MISONIDAZOLE AND DESMETHYLMISONIDAZOLE IN THE ISOLATED PERFUSED RAT LIVER.

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J Pharmacol Exp Ther; 219(3):669-674 1981

Dose-dependent clearance of misonidazole (MISO) and mechanism(s) involved in its clearance and that of its metabolite desmethylmisonidazole (DESMISO) was studied in isolated, perfused livers of male, Sprague-Dawley rats. Saturation kinetics were observed for both compounds. Initial concentrations (uM) of MISO in the perfusate were 74, 470, 1,500, 3,400 and 6,900; those for DESMISO were 15, 29, 77, 90 and 320. Elimination was followed for 180 min. For DESMISO, elimination from the perfusate was concentration dependent. Initial rates of disappearance at 80 uM or above were parallel, which suggested an apparent first order process. At lower concentrations of 1-20 uM, a saturable process was suggested. Similar kinetics were observed for MISO with first order elimination observed for 500 to 7,000 uM, with saturation suggested below 100 uM. The complete data sets are described by equations which are presented. Good correlation was shown between DESMISO perfusate concentrations (generated during the course of MISO perfusate perfusions) and simulations based on the MISO model which included microsomal data. The MISO and DESMISO models demonstrate that the relative contributions of the different pathways for elimination of the two compounds are strongly concentration-dependent and that the MISO via DESMISO pathway is a minor route. Qualitatively similar saturation kinetics was observed in the disappearance curves of both compounds from the liver perfusate. MISO in combination with excess DESMISO resulted in a marked decrease in clearance rate of MISO. This observation suggests that MISO and DESMISO are metabolized along similar pathways. (25 Refs)

25. DISPOSITION OF INDICINE N-OXIDE IN MICE AND MONKEYS.

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Cancer Treat Rep; 66(1):183-186 1982

The disposition of tritium-labeled indicine N-oxide (INO) was evaluated in mice and rhesus monkeys. Disappearance of INO from the serum of BDF1 mice given iv doses of 100 or 500 mg/kg occurred with an initial half-life of about 11 mins followed by a second phase greater than 100 mins. At 2 hrs after iv injection of mice, the highest concentrations of INO were present in kidney, liver, and intestine. In CDF1 mice bearing P388 leukemia cells and injected ip with a dose of 500 mg/kg, INO was found, in equal concentrations, in cells of the parent line, which is resistant to INO, and in cells of a line resistant to cyclophosphamide but sensitive to INO. Serum levels of INO in these mice decreased with an initial half-life of about 20 mins. For monkeys given iv doses of 24, 2.4, or 0.24 mg/kg, INO disappeared from the serum in three phases, with av half-lives of 3, 32, and 180 mins, respectively. Half-lives for the two observed phases of urinary excretion were 40 and 240 mins. In

24 hrs, both mice and monkeys excreted greater than 80% of the doses unchanged. (Author abstract) (9 Refs)

26. HEXAMETHYLMELAMINE AND PENTAMETHYLMELAMINE TISSUE DISTRIBUTION IN M5076/73A OVARIAN CANCER-BEARING MICE.

Broggini M, Rossi C, Colombo T, D'Incalci M
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Cancer Treat Rep; 66(1):127-133 1982

The distribution of hexamethylmelamine (HMM), pentamethylmelamine (PMM), and their metabolites N2,N2,N4,N6-tetramethylmelamine (TMM) and N2,N4,N6-trimethylmelamine (TriMM) was investigated in different tissues of M5076/73A ovarian cancer-bearing mice given 100 mg/kg ip of either drug. The area-under-the-curve (AUC) values of HMM and PMM, expressed in ug/g x min after these drug treatments, were 2,432 and 1,296 in tumor, 6,290 and 8,141 in liver, 9,779 and 21,294 in spleen, 6,840 and 10,800 in kidney, 4,003 and 4,295 in heart, 1,569 and 1,327 in brain, 163,689 and 50,809 in adipose tissue, 88,725 and 45,070 in lymph nodes, 15,033 and 18,992 in small intestine, and 393 and 351 in plasma, respectively. The elimination rate of HMM for the different organs was similar, with a half-life of 37-48 mins; PMM disappeared with more variability, the half-life being 19-46 min. While TMM concentrations were not very different from those of HMM or PMM, TriMM was much higher in all organs evaluated, particularly the brain, where AUC values were 21-24x those of the administered drug. (Author abstract) (16 Refs)

27. THE ROLE OF SUBCELLULAR LOCALIZATION IN ASSESSING THE CYTOTOXICITY OF IODINE-125 LABELED IODODEOXYURIDINE, IODOTAMOXIFEN, AND IODOANTIPYRINE.

Bloomer WD, McLaughlin WH, Weichselbaum RR, Hanson RN, Adelstein SJ, Seitz DE
Dept. Radiation Therapy, Harvard Medical Sch., Boston, MA
J Radioanal Chem; 65(1/2):209-221 1981

The role of subcellular localization in the cytotoxicity of 125I-bearing compounds was studied in vitro in the MCF-7 cell line of human breast cancer, which was derived from a malignant pleural effusion. Cell cultures were exposed to 125I-labeled tamoxifen (125ITAM), 125I-iodoantipyrine (125IAP), or 125I-iododeoxyuridine (125IUdR) at various concentrations. Cellular uptake of 125IUdR and 125IAP was directly proportional to media concentration of the compounds, with 125IUdR being more avidly accumulated than 125IAP. 125IUdR was incorporated directly into the DNA backbone as a thymidine analog; 125IAP was distributed according to body water. Uptake of 125ITAM was time dependent, with a steep initial rise followed by a plateau at 20 min, 37 C; at 4 C uptake was less steep, but linear. Withdrawal of 125ITAM from the medium was followed by a rapid efflux of unbound intracellular (IC) 125ITAM, leaving about 20% of 125ITAM activity within the cell after 50 min. The retained IC activity represented specifically and nonspecifically bound 125ITAM. With survival measured as a function of media concentration, D37 values were 8 x 10(-4) uCi/ml for 125IUdR, 2.3 uCi/ml for 125ITAM, and 68 uCi/ml for 125IAP. With survival measured as a function of protein- or nucleic acid-bound fractions, 125ITAM was approx as toxic as 125IUdR. Results indicate the importance of considering subcellular localization in determining the cytotoxic effects of Auger-emitting compounds. (43 Refs)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

28. PRETHERAPEUTIC TESTING OF ANTINEOPLASTIC DRUGS IN VITRO.

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Arch Geschwulstforsch; 52(1):1-7 1982

The in vitro sensitivity of solid human tumors (tumors of the breast, ovaries, lungs, and sarcoma) to daunoblastine, 5-fluorouracil, methotrexate, sarcolysin, trenimon, and vinblastine was studied by determining the residual 3H-thymidine uptake in DNA. The tumor tissue samples were incubated for 48 hr at 37 C. The correlation obtained between the in vitro sensitivity and the therapeutic results was not significant statistically. (7 Refs) (In GER)

29. THE INDUCTION OF DNA STRAND BREAKAGE BY NICKEL COMPOUNDS IN CULTURED CHINESE HAMSTER OVARY CELLS.

Robison SH, Costa M
Div. Toxicology, Dept. Pharmacology, Univ. Texas Medical Sch. Houston, P. O. Box 20708, Huston, TX, 77025
Cancer Lett; 15(1):35-40 1982

The effects of nickel chloride and crystalline NiS on the DNA of cultured Chinese hamster ovary (CHO) cells were studied by using alkaline sucrose gradient analysis. Both NiCl2 and crystalline alphaNiS induced DNA strand breaks in cultured CHO cells. Single strand breaks were detected in cells treated with either toxic or non-toxic levels of crystalline alpha NiS. Exposure to alpha NiS at 1 ug/ml for 24 hr does not interfere with the division of CHO cells. The level of cell plating efficiency was essentially similar to that of untreated cultures. This concentration caused substantial DNA strand breaks suggesting that crystalline alpha NiS selectively damages DNA. The positional shift in gradient sedimentation of the radiolabelled DNA fragments isolated from cells treated with either 1 ug.ml, or 5 ug/ml, or 20 ug/ml crystalline alphaNiS indicated the concentration-dependent effect on DNA strand breaks. Treatment of cells with NiCl2 at 1ug/ml, or 10 ug/ml also resulted in single strand breaks after only 2-hr exposure. Results suggest that nickel compounds which cause cellular transformation have highly selective and specific effects upon DNA structure since DNA strand breakage occurred at such low concentrations. (22 Refs)

30. GROWTH CHARACTERISTICS OF N-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]-FORMAMIDE (FANFT)-INDUCED MOUSE BLADDER TUMOR LINES IN A HUMAN TUMOR STEM CELL ASSAY.

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Cancer; 49(2):323-330 1982

Four N-[4-(5-nitro-2-furyl)-2-thiazolyl]-Formamide (FANFT)-induced mouse bladder tumor (MBT) lines were tested for their ability to form colonies in a tumor stem cell assay. Anticancer drug testing was done using this assay to determine whether reproducible colony survival curves could be produced. All four cell lines produced colonies at 10-14 days, whether taken from culture or murine tumor. Cloning efficiencies ranged from 0.29% to 1.93% from culture and from 0.005% to 0.05% from the murine source. Growth characteristics were described. Cells from colonies were histologically similar to the original cells plated. A linear relationship existed between the number of cells plated and the number of colonies produced. In vitro drug studies were reproducible and correlated with in vivo data. Therefore, MBT lines can be used for in vitro drug testing in a tumor stem cell assay and may be useful in selecting active chemotherapeutic agents in the murine tumor model. (Author abstract) (20 Refs)

31. ACTIVITY OF A NOVEL ANTHRACENYL BISHYDRAZONE, 9,10-ANTHRACENEDICARBOXALDEHYDE BIS[(4,5-DIHYDRO-1H-IMIDAZOL-2-YL)HYDRAZONE] DIHYDROCHLORIDE, AGAINST EXPERIMENTAL TUMORS IN MICE.

Citarella RV, Wallace RE, Murdock KC, Angier RB, Durr FE, Forbes M

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Cancer Res; 42(2):440-444 1982

The compound 9,10-Anthracenedicarboxaldehyde bis[(4,5-dihydro-1H-imidazole-2-yl)hydrazone] dihydrochloride (CL 216942; bisantrene hydrochloride; NSC 337766), a member of a new chemical class of compounds with antineoplastic properties, has been evaluated for antitumor activity in experimental murine tumor systems. The compound produced significant increases in life span (ILS) and long-term survivors among mice bearing transplantable leukemias and solid tumors. Optimal treatment regimens resulted in an ILS of greater than 173 and 151% in mice with P388 and L1210 leukemia, respectively, an ILS of greater than 85% in mice with Lieberman plasma cell tumor, and an ILS of greater than 200, 150, and 63%, respectively, in mice with B16 melanoma, colon tumor 26, and Ridgway osteogenic sarcoma. An Adriamycin-resistant subline of P388 leukemia showed complete cross-resistance to CL 216942. The compound was active when administered by the ip, iv, and sc routes, but po activity was not observed. Significant schedule dependency was not observed when the drug was administered once daily for 9 days, once every 4 days, or as a single dose, but single doses typically produced the best effects. CL 216942 was a potent inhibitor of DNA and RNA synthesis in L5178Y lymphoma cells cultured in vitro, and preliminary studies indicated the drug was a DNA-intercalating agent. The drug was cytotoxic for rapidly proliferating and nonproliferating (G0) human colon carcinoma WiDR cells in vitro. (Author abstract) (13 Refs)

32. 1-SUBSTITUTION DERIVATIVES OF 4-ARYL-2,3-DIBROMO-1-NAPHTHOL.

Krepelka J, Roubik J, Holubek J

Res. Inst. for Pharmacy and Biochemistry, 130 60 Prague 3, Czechoslovakia

Collect Czech Chem Commun; 46(9):2116-2122 1981

Preparation of a series of 1-substitution derivatives of 4-aryl-2,3-dibromo-1-naphthol is described. Preliminary pharmacological tests of 17 of the compounds indicate moderate antineoplastic activity similar to that of previously described compounds of this type. Compound II, an ethyl ester of omega-(7-ethyl-4-[4-ethylphenyl]2,3-dibromo-1 naphthyloxy)alkanoic acid, was most efficacious in various experimental tumor models. (8 Refs)

INTERFERON AND OTHER ANTIVIRALS

33. RAID SYNCYTIUM FORMATION INDUCED BY MOLONEY MURINE SARCOMA VIRUS IN 3T3/NIH CELLS AND ITS DELAY BY MOUSE INTERFERON.

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Arch Virol; 70(2):103-114 1981

Moloney murine sarcoma virus (MSV) clone 124 was found to induce rapid syncytium formation upon infection of 3T3/NIH at a high multiplicity of infection. This effect became apparent, by light microscopy, within 1 to 2 hr, whereas by scanning electron microscopy, clusters of 4 to 25 cells were seen in their initial steps of syncytium formation within 20 to 30 min after virus addition. It appeared that the cell fusion was initiated by connection between the cells through virus bound to their surface. After a few more hr several neighboring syncytia fused into giant cells containing over a hundred nuclei. Though MSV (124) stocks contained also some MLV it appeared that the syncytium inducing activity was related to the MSV particles. MLV particles were not only incapable to induce syncytium formation, they even interfered with this activity of MSV. The MSV-induced cell fusion required the adsorption of intact virions, but was independent on protein synthesis. Mouse interferon remarkably reduced the rate of syncytium development. (Author abstract) (40 Refs)

34. ASSAYS TO MEASURE PLASMA MEMBRANE AND CYTOSKELETAL CHANGES IN INTERFERON-TREATED CELLS.

Pfeffer LM, Wang E, Landsberger FR, Tamm I

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Methods Enzymol; 79:461-473 1981

Techniques were described for the measurement of interferon (IF)-induced changes in cell size, cytoskeleton, cell surface fibronectin distribution, lateral mobility of cell surface receptors, and fluidity of the plasma membrane. Cell surface area of human diploid fibroblasts (between passages 10-20) was measured with the use of photomicrographs; cell vol was determined by a Coulter H4 Channelyzer. Cells treated with IF were more heterogeneous than control cells as indicated by greater coefficient of variation (21.5% vs 11.5%) of the cell vol distribution. Indirect immunofluorescence staining of microtubules, 10-nanometer filaments, microfilaments, and fibronectin of human fibroblasts was also discussed. Human HeLaS3 cells were used to show the effect of IF on lateral mobility of cell surface receptors for fluorescein-conjugated concanavalin A, which was examined by epifluorescence microscopy. In IF-treated cells incubated at 37 C, the fluorescence remains patchy and does not tend to form a cap, as occurs in control cells. The use of electron spin resonance techniques plus probe molecules (spin labels) to study the influence of IF on structure of the plasma membrane lipid bilayer in HeLaS3 cells and human fibroblasts was also discussed, with comments on some technical details and interpretation of the resulting spectra. (20 Refs)

35. ENHANCED EXPRESSION OF MELANOMA-ASSOCIATED ANTIGENS AND BETA2-MICROGLOBULIN ON CULTURED HUMAN MELANOMA CELLS BY INTERFERON.

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JNCI; 68(1):19-25 1982

The effect of human leukocyte interferon (IFN) on the in vitro growth and expression of melanoma-associated antigens (MAA), beta2-microglobulin (beta2m) and HLA-DR antigen on cultured human melanoma cells was studied. Exposure of melanoma cells to IFN for 64 hours resulted in a dose-dependent inhibition of growth with 46% reduction in cell number at 10(3) U IFN/ml and 74% reduction at 10(5) U/ml. Quantitative absorption experiments in the mixed hemadsorption assay determined that the expression of MAA and beta2m on treated cells was enhanced at 10(2) -10(5) U IFN/ml, twofold to fivefold for MAA and fivefold to twelvefold for beta2m. No change was seen in HLA-DR antigen expression. The IFN-induced enhancement of MAA and beta2m could be detected as early as after 16 hours and a maximum expression was reached at 96 hours after IFN exposure. The IFN-induced enhancement of MAA and beta2m on melanoma cells was reversible. Studies with melanoma cells grown in stationary phase and serum-deprived conditions indicated that IFN-induced augmentation of MAA and beta2m did not require cell proliferation. The data suggest that the effect of IFN on antigen expression is independent of its effect on cell growth. Further studies are needed to fully elucidate the mechanism. (Author abstract) (42 Refs)

36. REVIEW OF EXPERIENCE WITH INTERFERON AND DRUG SENSITIVITY TESTING OVARIAN CARCINOMA IN SEMISOLID AGAR CULTURE.

Epstein LB, Marcus SG

Cancer Res. Inst., Univ. California, San Francisco, CA, 94143

Cancer Chemother Pharmacol; 6(3):273-277 1981

Studies were performed with a semisolid agar culture system to determine the in vitro sensitivity of human ovarian carcinoma to human leukocyte interferon (IFN-alpha) and standard chemotherapeutic agents (adriamycin, cis-platinum, hexamethylmelamine, melphalan, and velban). Growth in culture occurred in 67% of samples derived from ascitic fluid. Seventy-one percent of samples exhibited reduction in tumor colony number greater than 25% in response to 300 units IFN/ml. The responsiveness of the tumor cells to interferon ran parallel to their overall responsiveness to the other chemotherapeutic agents. Sensitivity to interferon was not related to the histology or grade of the tumor or to the stage of the disease. The mean value for the percentage of viable cells in the ascitic samples (89%) was considerably higher than in solid tumor samples (39%). The mean percentage of tumor cells in the ascitic samples (28%) was considerably lower than of the solid tumor samples (81%). Colonies from ascitic fluid were more sensitive to the antiproliferative effects of interferon than the colonies form solid tumor samples. Analysis of drug testing showed that in 58% of 12 evaluable situations when a positive response in vitro was given, stabilization or regression of the tumor occurred in vivo after treatment with the drug. The studies could be used for assessing whether various types of interferon have the same degree, range, and mechanism of action of antitumor effect. (18 Refs)

OTHER RELATED STUDIES

37. CHEMOTHERAPY FOR TUMOURS USING CLOSTRIDIAL ONCOLYSIS, ANTIBIOTICS AND CYCLOPHOSPHAMIDE: MODEL TRIAL ON THE UVT 15264 TUMOUR.

Schlechte H, Schwabe K, Mehnert WH, Schulze B, Brauniger H
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Arch Geschwulstforsch; 52(1):41-48 1982

Lysis of tumor cells by Clostridium butyricum H8, as well as possible synergistic effects of antibiotics and/or chemotherapy, were studied. UV-induced murine spindle-cell tumors (UVT 15264) were maintained by im transplantation in the 17/Berlin-Buch mouse strain. Oncolysis was induced by iv injection of 1.25 x 10(8) bacterial spores into tumor-bearing mice. Antibiotic combinations were administered to limit or entirely eliminate bacterial growth. Cyclophosphamide (CPA: 1.5 mg) was administered to some animals on days 3 and 7 after spore injection. Spore treatment (ST) alone produced oncolysis afte approx 3 days, with an av survival time (AST) of 27 days, compared with an AST of 36 days for untreated controls. The combination of ST with subthreshold inhibitory antibiotic therapy produced oncolysis lasting 5 days and an AST of 41 days. Higher doses of antibiotics reduced oncolysis without changing AST relative to controls . CPA produced an AST of 46 days. Combining ST and CPA produced marked tumor regression, indicating that the two therapies act on different areas of the tumor; AST, however, was shortened to 38 days. Combining ST, CPA, and antibiotic therapy shortened AST to 29 days but did not produce tumor regression greater than ST plus CPA. (30 Refs)

38. STRUCTURE-ACTIVITY RELATIONSHIPS OF ANTHRACYCLINES RELATIVE TO CYTOTOXICITY AND EFFECTS ON MACROMOLECULAR SYNTHESIS IN L1210 LEUKEMIA CELLS.

Matsuzawa Y, Oki T, Takeuchi T, Umezawa H
Central Res. Lab., Sanraku-Ocean Co., Ltd., 4-9-1 Johnan, Fujisawa, Kanagawa 251, Japan
J Antibiot (Tokyo); 34(12):1596-1607 1981

The effects of 92 anthracycline compounds on the growth and DNA, RNA and protein synthesis of L1210 leukemia cells were studied in relationships to their structures and antitumor activity. The hydroxyl groups at C-1, C-2, C-4, C-6, and C-11 on aglycones have significant relationships to the in vitro potency. Compounds lacking the hydroxyl group at C-6 or containing the methoxyl group at C-6 are lower in their cytotoxicity and RNA and DNA synthesis-inhibiting activity than those containing the C-6 hydroxyl group. The hydroxyl group at C-2 did not influence the in vitro potency, but the hydroxyl group at C-1 and/or C-11 enhanced the potency. The activity which prolongs the life span of L1210-bearing mice was decreased by an hydroxyl group at C-1 or C-11, although the effective doses were lowered. In compounds which are different at C-4, in vitro potency increased in the following series: deoxy greater than hydroxy greater than methoxy. The side chain at C-9 in aklavinone- and daunomycinone-glycosides produced slight influence on cytotoxicity and on the activity which inhibits RNA and DNA synthesis in intact cells. Ethyl, isopropyl and acetonyl derivatives at C-9 had an equal potency. The methyl derivative had the least activity. A 10-carbomethoxy group in the S-configuration decreased the inhibitory activity on RNA synthesis. The removal of this group at C-10 resulted in a marked reduction in cytoxicity and in the activity which inhibits nucleic acid synthesis. The amino function either on the aglycone or on the sugar moiety was essential for in vitro activity. Compounds having an alkylamino group at C-3' were more potent in vitro than those with a primary amino group, although these groups produced different effects in in vivo activity, depending on each anthracycline. Disaccharides and trisaccharides were more potent in vitro than monosaccharides. The length of the sugar chain did not correlate with in vivo antitumor activity. (31 Refs)

39. EFFECTS OF VASOPRESSIN, NORADRENALIN AND OXYTOCIN ON BLOOD FLOW DISTRIBUTION IN RAT KIDNEY WITH NEOPLASM.

Tvete S, Gothlin J, Lekven J

Dept. Diagnostic Radiology, Haukeland Sykehus, N-5016 Bergen, Norway

Acta Radiol Oncol Radiat Phys Biol; 20(4):253-260 1981

The arterial blood flow distribution between tumor and intact renal tissue was investigated in rats with transplanted sarcomas. Changes in tissue flow were measured by the microsphere tracer technique, and the redistributing effects on blood flow of vasopressin, noradrenalin and oxytocin was recorded. Bolus injections of vasopressin gave a transient decrease of intact tissue flow, not found in tumors. At increasing doses of vasopressin and in early tumor growth phase, the flow discriminating effect tended to vanish. Constant intravenous infusion of vasopressin gave similar reduction of flow in tumor and intact Tissue. Selective administration into the renal artery reduced flow in intact tissue but produced ambiguous effects in tumor tissue. Noradrenalin produced less reduction of tumor flow as compared with intact tissue flow. Oxytocin increased tumor blood flow while no flow change occurred in intact tissue. Oxytocin thus appeared to produce the most favorable redistribution of flow within tumor kidneys for the prospect of conveying cytotoxic agents selectively to the tumor. (Author abstract) (24 Refs)

40. ADRIAMYCIN-INDUCED CHANGES IN THE SURFACE MEMBRANE OF SARCOMA 180 ASCITES CELLS.

Murphree SA, Tritton TR, Smith PL, Sartorelli AC

Dept. Pharmacology and Developmental Therapeutics Program, Comprehensive Cancer Center, Yale Univ. Sch. Medicine, New Haven, CT, 06510

Biochim Biophys Acta; 649(2):317-324 1981

Adriamycin increases (a) the rate of agglutination of Sarcoma 180 cells by concanavalin A after brief exposure of 2-3 hr and (b) membrane fluidity as measured by ESR within 30 min of exposure at concentrations of the anthracycline at 10(-7)-10(-5) M. The effect of adriamycin on agglutination is not due to an increase in the number of surface receptors for concanavalin A, since the extent of binding of the lectin is not altered by adriamycin and no change occurs in the rate of occupancy of the concanavalin A binding sites by the lectin in cells treated with the antibiotic. The order parameter, a measurement of membrane fluidity, decreases in cells exposed to adriamycin and is dose-related. The results indicate that adriamycin can induce changes in the surface membrane of Sarcoma 180 cells within a brief period of exposure to a low but cytotoxic level of this agent. (Author abstract) (39 Refs)

41. INFLUENCE OF PYRAZOFURIN ON THE TOXICITY AND ANTITUMOR ACTIVITY OF FLUORINATED PYRIMIDINES IN VIVO.

Johnson RK, Howard WS, Faucette LF, Wodinsky I, Clement JJ
Arthur D. Little, Inc., Cambridge, MA
Adv Enzyme Regul; 19:309-333 1981

We undertook to evaluate the interaction of pyrazofurin (PF) with another important pyrimidine antimetabolite, 5-fluorouracil (5-FU). 5-FU can be anabolized to the nucleoside monophosphate by three pathways, directly via phosphoribosylation by orotate phosphoribosyltransferase (EC 2.4.2.10), or via the salvage pathways, by either uridine phosphorylase (EC 2.4.2.3) and uridine kinase or thymidine phosphorylase (EC 2.4.2.4) and thymidine kinase (EC 2.7.1.21). One might expect that depletion of pyrimidine nucleotides by PF might enhance the anabolism of 5-FU and allow for greater incorporation of 5-FU into RNA and/or lead to higher levels of 5-fluoro-2'-deoxyuridylate (FdUMP) with subsequent greater inhibition of thymidylate synthase (EC 2.1.1.45). This was, however, not the case. One the contrary, PF markedly decreased the toxicity of 5-FU and blocked its antitumor activity in some tumors as well. With the closely related compound, 5-fluorouridine (FUR), the interaction with PF was the opposite; there was a marked enhancement of both toxicity and antitumor activity similar to that seen with 5-ACr. (46 Refs)

42. MONSTROUS CELL IN MALIGNANT GLIOMAS: IN RELATION TO RADIATION AND CHEMOTHERAPY.

Ogashiwa M, Takeuchi K, Akai K
Dept. Neurosurgery, Kyorin Univ., Sch. Medicine, Mitaka-shi, Tokyo 181, Japan
No To Shinkei; 33(7):733-742 1981

The pathological effects of irradiation and chemotherapy in nine autopsied cases of malignant and low grade gliomas were studied. The brains were examined by the complete study technique. Many histological features were related to surgery, grading of histological classification of the gliomas, irradiation and chemotherapy. Following irradiation and chemotherapy, in addition to increased necrosis and vascular response, a variety of characteristic changes were observed in cellular and nuclear morphology with pronounced formation of monstrous cells in all of five malignant gliomas treated with nitrosourea. These monstrous cells had irregular and hyperchromatic multinuclei and showed cytoplasmic degeneration. These cells, which had no direct relationship to vessels, were distributed both in the periphery of the tumor or the necrotic areas and in the white matter remote from the main tumor. These changes were more pronounced in autopsy specimens than in biopsy specimens. These features indicate that the monstrous cells may appear as a result of inhibition of tumor cell division at the late mitotic phase after irradiation and chemotherapy. (22 Refs) (In JPN)

43. NK CELL SENSITIVITY OF THE LEUKEMIC K 562 CELLS; EFFECT OF SODIUM BUTYRATE AND HEMIN INDUCTION.

Dokhelar MC, Testa U, Vainchenker W, Finale Y, Tetaud C, Salem P, Tursz T
(c/o Tursz), Institut Gustave-Roussy, Rue Camille Desmoulins, 94800 Villejuif, France
J Immunol; 128(1):211-216 1982

Two differentiation inducers, hemin and sodium butyrate, have been studied for their effect on the NK sensitivity of human leukemic K 562 cells. When cultivated in the presence of 0. 1 mM hemin, K 562 cells increased their hemoglobin synthesis. However, their susceptibility to NK lysis remained unaffected. On the other hand, sodium butyrate, which is known as a more potent differentiating agent, consistently reduced the NK sensitivity of K 562 cells and simultaneously induced the appearance of several differentiation markers. The effect of sodium butyrate on NK sensitivity was dose-dependent (maximal action at a 2-mM concentration), appeared after 2 days in culture, and was maximal after 5 days. After sodium butyrate removal from the culture medium, K 562 cells recovered their normal NK susceptibility within 4 days. In cold-target competition experiments, untreated K 562 cells acted as better competitors than butyrate-treated K 562 cells. Target-binding cell assays and specific NK cell removal on K 562 monolayers demonstrated that NK cells were less adherent to butyrate-treated than to control K 562 cells. From these data, it could be postulated that sodium butyrate modulates the expression of some target structure(s) involved in NK target binding. Five subclones of K 562 have been selected for exhibiting distinct, stable properties with regard to their cellular commitment (either to erythroid or to megakaryocytic lineage). The NK sensitivity of these subclones was roughly identical, and in all of them, butyrate treatment induced similar protection against NK-mediated lysis. Thus, the susceptibility to NK lysis and its modulation did not depend upon the predominant lineage present in each clone. (Author abstract) (32 Refs)

44. INHIBITION OF GROWTH OF 3-METHYLCHOLANTHRENE-INDUCED MOUSE SKIN TUMOR BY PROTEASE INHIBITOR [N,N-DIMETHYLCARBAMOYLMETHYL 4-(4-GUANIDINOBENZOYLOXY)-PHENYLACETATE] METHANESULFATE.

Ohkoshi M
Dept. Oral Surgery, Nagoya Univ. Sch. Medicine, 65, Tsurumai-cho, Showa-ku, Nagoya 466, Japan
Gan; 72(6):959-964 1981

A 3-Methylcholanthrene-induced tumor was challenged with a low molecular synthetic protease inhibitor, [N,N-dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy)-phenylacetate] methanesulfate. This drug at a dosage of 10 mg/kg or 20 mg/kg was administered by ip injection to 20 mice each harboring a solitary tumor twice daily for 10 wk. This protease inhibitor significantly inhibited tumor growth and prolonged the survival time of the tumor-bearing mice (p less than 0.001). The results suggest the involvement of kinin-forming proteases, such as trypsin, plasmin and kallikrein, in the tumor growth. (Author abstract) (16 Refs)

45. INCREASES IN PROTEIN A24 FOLLOWING TREATMENT OF EHRLICH ASCITES TUMOR CELLS WITH 1-METHYL-1-NITROSOUREA AND 1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA.

Dornish JM, Smith-Kielland I
Dept. Biochemistry, Univ. Oslo, Blindern, Oslo 3, Norway
FEBS Lett; 136(1):41-44 1981

Following treatment of Ehrlich ascites cells with 1-methyl-1-nitrosourea (MNU) a nd 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), densitometric analysis of one-dimensional gels revealed that protein A24 (a conjugate of histone H2A a ubiquitin) increased in a dose-dependent manner, while protein synthesis was totally inhibited. Treatment of cells with 50 ug/ml BCNU led to 247x more A24 than in control cells. Treatment with 200 ug/ml MNU led to 307x more A24 than in controls. Increases of protein A24 were also demonstrated by two-dimensional gel electrophoresis. The simultaneous presence of puromycin (20 ug/ml) had no effect of protein A24, indicating that protein synthesis was not responsible for the larger amounts of A24 seen after nitrosourea treatment. Possible ways in which nitrosoureas could cause the apparent increases in protein A24 included alkylation by BCNU and MNU changing the structure of protein A24 and preventing its cleavage mediated by A24 lyase, preventing A24 cleavage through DNA crosslinking, or inhibition of A24 lyase nitrosourea-treated cells. (23 Refs)

46. THE EFFECTS OF LEVONANTRADOL HYDROCHLORIDE ON TUMOR GROWTH AND THERAPY.

Wolff JS, Hemsworth GR, DeMaio M, Sloan D
Pfizer Central Res., Groton, CT, 06340
J Clin Pharmacol; 21(Suppl8/9):99S-102S 1981

Effects of levonantradol hydrochloride (LEV) on the course of chemotherapy and on the tumor growth in three models in mice were investigated. Female C57Bl/6 DBA/2 (B6D2F1) mice were hosts for the B-16 melanoma and L-1210 leukemia and the source of peritoneal exudate cells. Female CD-1 mice were host for sarcoma 180J tumor. Mice inoculated ip with 1 x 10(6) sarcoma 180J cells survived for 17.8 +-4.0 days. The ip administration of 0.1, 0.5, or 2.5 mg/kg LEV 21, 27, and 48 hr after tumor inoculation, had no effect on the death rate. Ip inoculation of 75 mg/kg cyclophosphamide (CY) 1 day after initiation of the ascitic tumor resulted in a 135% increase in survival; this effect was neither enhanced nor diminished by LEV administered 3 hr before and 3 and 24 hr after CY administration. LEV administration 27 and 48 hr after inoculation of mice with 1 x 10(5) L1210 leukemia cells did not affect the 7.7 +-1.1 day survival of the mice. CY (150 mg/kg ip 24 hr after tumor inoculation) increased survival of L-1210-bearing mice by 196% (15.1 +-1.6 days); this effect was not altered by LEV given 3 and 24 hr after CY. The incidence and extent of metastases on the lung surface 19 days after inoculation of B-16 melanoma (line F-10) cells was not affected by administration of LEV 1 day prior to or 1 day after tumor cell inoculation. Macrophages obtained from mice 4 days after ip injection of LEV were not activated. These preliminary rodent studies failed to demonstrate any effect of LEV under the conditions used. (9 Refs)

47. CHANGES IN THYMUS FACTOR LEVEL IN RATS WITH JENSEN SARCOMA AND THE INFLUENCE OF APPLICATION OF THYMUS HORMONE ON TUMOR GROWTH RATE.

Busse E, Rose H
Geschwulstklinik (Charite), Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
Z Exp Chir; 14(5):306-309 1981

Changes in the plasma levels of thymus factor (TF) and the effects of various treatments were studied in Wistar rats bearing transplanted Jensen sarcomas. Adult rats (90-110 g) were injected in the thigh with 10(8) tumor cells. TF levels were determined 16 days after transplantation (TP). The following treatments were used singly or in various combinations: (1) Local irradiation (RT) was begun 2 days after TP with a total dose of 21 Gray (3 Gray/day for 5 days, 2 days pause, and 3 Grays/day for 2 days). (2) Cyclic AMP levels were raised by ip injection of l-dihydroxyphenylalanine (l-DOPA: 100 mg/kg, 3 x/day for 6 days, followed by 1 x or 2 x/day for 6 days). (3) Interferon production was induced by injection of measles vaccine (MV: 10,000 TCD50/day im on days 1, 3, and 5 after TP).

(4) TF was injected ip (0.2 ml 2 x/day, for 12 days, beginning 1 day after TP). The lowest rate of tumor growth was obtained with a combination of RT, l-DOPA, and MV (11/13 rats tumor-free). All tumor-bearing animals showed lower plasma TF levels (107-119 units) than tumor-free animals (188-239 units). Animals responding to treatment had TF levels comparable to untreated, tumor-free controls. TF treatment alone and a combination of l-DOPA and MV reduced tumor growth significantly. (20 Refs) (In GER)

48. TREATMENT OF NON SEMINOMATOUS TESTICULAR TUMORS.

Olier C

Service d'Urologie, Centre Hospitalier Universitaire Saint-Jacques, 28, place Henri-Dunant, 63000 Clermont-Ferrand, France

Sem Hop Paris; 57(47/48):2039-2045 1981

Progress in the diagnosis and treatment of NSTT has been registered during the last years. Tumor markers have lowered the percentage of staging error; nevertheless they have their limits and a return to normal of tumor markers does not mean the obligatory disappearance of a viable tumor. The treatment of NSTT is an emergency: lymphadenectomy is now, for most authors limited and guided by extemporaneal exploration; radiotherapy has a complementary target of detecting agent; chemotherapy (particularly since CDDP was introduced) is very efficient in disseminated forms of disease giving long term remission in 50 to 70% of cases. Actual results give, for the next years, the hope of eradication of NSTT in a high number of cases. (Author abstract) (30 Refs) (In FRE)

49. LYMPHOTOXIN CYTOTOXICITY, A COMBINATION OF CYTOLYTIC AND CYTOSTATIC CELLULAR RESPONSES.

Evans CH, Heinbaugh JA

Tumor Biology Section, NCI, Room 2A-17, Building 37, Bethesda, MD, 20205

Immunopharmacology; 3(4):347-359 1981

The extent to which cytostatic and cytolytic cellular responses are responsible for or contribute to the widely divergent susceptibilities of tumor cells to lymphotoxin was investigated . Observed patterns of 51Chromium release preceding 3Hydrogen with equivalent total release for the two radionuclides were consistent with cytolytic destruction of alphaL929 cells by guinea pig lymphotoxin. Similar results were obtained with antigen- or mitogen-induced guinea pig lymphotoxin. L929M cells were less sensitive and L929, 2071, L1210 and 104C1 cells were resistant to cytolytic activity of guinea pig lymphotoxin. Growth inhibition of alphaL929 cells by lymphotoxin was found to be due to cytolytic mechanisms, while that of 104C1 cells was found to be due to cytostatic mechanisms. Cytostatic responses to lymphotoxin could be reversed upon replenishment with lymphotoxin-free medium. These results indicate that cellular responses to lymphotoxin are complex and consist of both cytolytic and cytostatic components. Only cytostatic responses are potentially reversible. (24 Refs)

50. IMMUNOGENICITY AND CROSS-PROTECTION AMONG B16 MELANOMA VARIANTS WITH DIFFERING PROCLIVITIES TO METASTASIZE.

Harte PJ, Steele G, Munroe AE, Rayner AA, Wang BS, Wilson RE, Mannick JA

(c/o Steele), Brigham and Women's Hosp., 75 Francis St., Boston, MA, 02115

J Surg Oncol; 18(4):381-388 1981

We report here the lack of any relationship between immunogenicity and the potential to metastasize among four B16 melanoma variants. Groups of C57BL/6J mice were immunized with one of four B16 variant lines (maintained by serial IM passage) that were shown in separate experiments to produce the following incidences of pulmonary metastases 4 to 6 wk after isograft excision: M1, 10%-15%; M2, 10%-20%; M3, 75%-80%; and M4, 75%-90%. After immunization, mice were challenged with one of the four variant lines in a crisscross fashion. Two challenge doses for each line were chosen on the basis of earlier experiments showing 100% and 50% challenge tumor take in nonimmunized animals. Despite earlier work published from this laboratory showing that splenocytes harvested from immunized mice could distinguish antigenic differences among the B16 variants, we could find no significant difference in immunogenicity or cross-protection among the lines regardless of their metastatic potential. We conclude that no correlation exists between the antigenic differences shown by in vitro splenocyte-mediated cytotoxicity assays among the B16 variants and in vivo immunogenicity or cross-protection experiments. Furthermore, the relationship (if any) between immunogenicity and the ability to metastasize among these B16 variants is not straightforward. (Author abstract) (11 Refs)

51. CHLORPROMAZINE DISTRIBUTION IN HAMSTERS AND MICE BEARING TRANSPLANTABLE MELANOMA.

Fairchild RG, Greenberg D, Watts KP, Packer S, Atkins HL, Som P, Hannon SJ, Brill AB, Fand I, McNally WP

Medical Dept., Brookhaven Natl. Lab., Upton, NY, 11973

Cancer Res; 42(2):556-562 1982

Chlorpromazine (CPZ) distribution was measured in tissues of Syrian golden hamsters bearing Greene melanoma and in BALB/c mice bearing Harding-Passey melanoma. Distribution was evaluated as a function of time (0.5 to 14 days) and as a function of single and multiple doses (up to 5) of from 5 to 50 mg CPZ per kg body wt. Routes of administration (ip, iv, po) were compared. The physiological behavior of CPZ is of interest as it is used extensively as a tranquilizing drug (Thorazine). Further, since CPZ binds to the pigment melanin, the possibility exists of using CPZ to transport diagnostic or therapeutic agents to melanoma. It was found that, at 2 days postinjection, tumor/tissue concentration ratios exceeded 10 for metabolizing organs, such as liver, and 100 for 'background' tissues, such as blood and muscle. Absolute concentrations of CPZ in tumor exceeding 100 ug CPZ per g tumor were obtained with both single and multiple doses. This selective high concentration in tumor would make CPZ an ideal vehicle for the transport of boron to tumor for use in neutron capture therapy via the 10B(n,alpha)7Li reaction. (Author abstract) (37 Refs)

52. IN VIVO KINETICS OF THYMIDYLATE SYNTHETASE INHIBITION IN 5-FLUOROURACIL-SENSITIVE AND -RESISTANT MURINE COLON ADENOCARCINOMAS.

Spears CP, Shahinian AH, Moran RG, Heidelberger C, Corbett TH (c/o Heidelberger), Univ. Southern California Cancer Center, 1721 Griffin Ave., Los Angeles, CA, 90031
Cancer Res; 42(2):450-456 1982

The predictive utility of several biochemical parameters of 5-fluorouracil (5-FUra) action was evaluated in four murine colonic adenocarcinomas: 5-FUra-sensitive tumor 38 and 5-FUra-resistant tumors 07/A, 51, and 06/A. Thymidylate synthetase (TS) was determined by a tritiated 5-fluoro-2'-deoxyuridylate (FdUMP)-binding assay. Bolus 5-FUra (80 mg/kg, ip) administration caused in all tumors a rapid decrease in free TS levels. Only tumor 38, however, showed inhibition of TS to undetectable (less than 0.05 pmol/g) levels, which lasted up to 6 hr after treatment; correction for dissociation of endogenous TS; FdUMP:folate ternary complex during the TS assay was required. Total TS (free enzyme plus ternary complex) was determined with experimental conditions that achieved quantitative recovery of free TS from ternary complex. By 48 hr after 5-FUra, Tumor 38 showed a decrease in total TS proportional to the estimated log kill/dose of 5-FUra; in contrast, the resistant tumors showed no such decrease from pretreatment levels. Assay of FdUMP showed that the free nucleotide was formed rapidly in all tumors in excess over available TS-binding sites. However, tumor sensitivity did not correlate with peak or residual FdUMP levels or with deoxyuridylate levels, which were low and remained so in all tumors. Tumor sensitivity to 5-FUra also could not be explained by the small differences among the tumors in total perchloric acid-soluble metabolites of 5-FUra or drug incorporation into RNA. We conclude from these data that levels of free TS in the tumor after 5-FUra treatment are predictive of chemotherapeutic response in these murine models of human colonic adenocarcinoma. (Author abstract) (50 Refs)

53. EFFECT OF COMBINED MISONIDAZOLE AND ACCELERATED NEON IONS ON A HUMAN MELANOMA TRANSPLANTED INTO NUDE MICE.

Guichard M, Tenforde T, Curtis S, Malaise EP

Institut de Radiobiologie Clinique, Institut Gustave-Roussy, 16 bis, Avenue Paul-Vaillant Couturier, 94800 villejuif, France

Radiology; 142(1):219-223 1982

The response to accelerated neon ions of human Nall melanomas growing in nude mice was measured by an in vitro colony-forming assay following in situ tumor irradiation in the midposition of a 10-cm extended-peak ionization region. Values of the relative biological effectiveness (RBE) for peak neon ions compared with 60Co gamma radiation were 3.2 and 3.4, respectively, at the 1% and 10% survival levels. Following irradiation with peak neon ions, the repair of potentially lethal damage (PLD) was comparable to that observed after gamma irradiation. When misonidazole (1 mg/g intraperitoneal dose) was administered in combination with extended-peak neon ions, the drug enhancement ratio (ER) at the 1% survival level was 1.5 if the tumors were removed and plated in vitro immediately following irradiation, and 1.9 if tumor excision and plating were delayed for greater than or equal to 6 hr. Administration of misonidazole completely inhibited PLD repair following either gamma irradiation or extended peak neon-ion irradiation. (Author abstract) (18 Refs)

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ICRDB CANCERGRAM

ANTITUMOR AND ANTIVIRAL AGENTS

Experimental Therapeutics, Toxicology, Pharmacology

SERIES CB20 No. 82/06

JUNE, 1982

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ANTITUMOR AGENT EFFICACY IN VIVO

1. EFFECT OF 3'-AMINO-3'-DEOXYTHYMIDINE ON L1210 AND P388 LEUKEMIAS IN MICE.

Lin TS, Fischer PH, Prusoff WH
Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Biochem Pharmacol; 31(1):125-128 1982

The therapeutic efficacy of 3'-amino-3'-deoxythymidine (ADT) was studied in CDF1 mice bearing L1210 leukemia. Mice received ADT ip 24 hr after tumor transplantation, with

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subsequent doses according to different schedules. Daily administration of ADT on days 1-6 resulted in a dose-dependent increase in life span (from 11% after 40 mg/kg to 72% after 320 mg/kg). The antileukemic effect of ADT was improved markedly after bid administration for 3 days (144% increase in the lifespan after 160 mg/kg and 128% increase after 320 mg/kg). The tid administration on day 1 of 160 or 320 mg/kg resulted only in 12-19% increase in lifespan. The curative schedule was associated with minimal toxicity. ADT was less effective against P388 leukemia: bid administration of 150, 300, or 600 mg/kg produced 22, 22, and 33% increases in lifespan, respectively. (9 Refs)

2. COMPARATIVE STUDIES ON ANTI-TUMOR EFFECTS OF NITROSOUREAS, ACNU AND MCNU, ON EXPERIMENTAL BRAIN TUMORS.

Harada K, Kiya K, Okamoto H, Uozumi T
Dept. Neurosurgery, Hiroshima Univ., Hiroshima 734, Japan
Neurol Med Chir (Tokyo); 21(10):1017-1023 1981

Comparative anti-tumor effects of ACNU (1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2 chloroethyl)-3 nitrosourea) and MCNU were studied on 20-methylcholanthrene-induced C57 black mouse malignant gliomas (MG-cells) and rat glial tumors (C6-cells) in vitro and in vivo. The inhibitory effects of ACNU and MCNU in vitro were dependent on dose and time. The concentration showing inhibitory effect was more than 10 ug/ml. ACNU was slightly more effective than MCNU. ACNU significantly inhibited DNA synthesis at concentrations higher than 10 ug/ml, but had no such effect on RNA and protein syntheses. MCNU also inhibited DNA synthesis similar to but less than that of ACNU. By a single intraperitoneal administration on day 5, an increased life span (ILS) was observed with ACNU (120.3% increase) and with MCNU (100.4%). The optimal dose was 25 mg/kg/day for both drugs. The therapeutic ratio, or optimal dose divided by the dose producing an increased life span of 30% over controls, of ACNU was 4.17 and that of MCNU was 6.67. When 25 mg/kg/day of ACNU was administered intraperitoneally on day 5, 2 out of 10 mice survived over 60 days. In case of MCNU, 1 out of 10 mice survived. A single administration of ACNU or MCNU was more effective for the increased life span compared with intermittent administration. From these results, it is suggested that the new water soluble nitrosourea, MCNU, can be utilized as a chemotherapeutic agent against brain tumors as in the case of ACNU. (Author abstract) (28 Refs) (In JPN)

3. COMPARISON OF CYTOTOXIC ACTION OF IPHOSPHAMIDE AND CYCLOPHOSPHAMIDE.

Phelan ET, Vietti TJ, Valeriote FA, Coulter D
(c/o Valeriote) Section Cancer Biology, Washington Univ. Sch. Medicine, 4511 Forest Park Blvd., Room 405, St. Louis, MO, 63108
Anticancer Res; 1(3):149-153 1981

Cytotoxic effects of iphosphamide (IP) and cyclophosphamide (CY) were investigated with respect to the mode of administration on transplanted L1210 leukemia cells and normal hematopoietic stem cells in the femoral marrow of CDF1 mice. The quantitative spleen colony assay was used to study normal hematopoietic colony-forming units (NCFU) and L1210 leukemia colony-forming units (LCFU). The drugs were administered iv either in 0.51 ml single doses or over a period of 24 hr in a vol of 2.5 ml by infusion. The LCFU dose-survival curves for IP and CY were similar with an exponential decrease in survival with increasing dose and a D 1/2 (dose required to reduce survival by 50%) of 0.1 mg/mouse. The NCFU for IP and CY was different: both generated exponential dose-survival curves, but the D 1/2 values were 3.3 mg/mouse for IP and 1.7 mg/mouse for CY. Similar survival rates were observed after administration of single doses of IP and CY. When administered as infusions, dose-survival curves for both drugs were similar with a D 1/2 value of 0.17 mg/mouse. Infusion of either drug resulted in decreased cytotoxicity by a factor of 1.7. When increasing doses of drugs were given either as an infusion or as a single dose to normal CDF1 mice, a mean LD50 for single-dose CY of 7.2 +-1.3 mg/mouse was found, while for an infusion this value increased to 11 +-2.4 mg/mouse. For IP, the mean LD50 values were 18.5 +-4.5 mg/mouse after single dose and 25 +-6.6 mg/mouse for infusion. Cytotoxicity decreased as infusion time increased, and there was a 50% decrease in effectiveness of CY for each 2.7-hr increase in the duration of infusion. IP was therapeutic at doses up to 2x those of CY, indicating that IP is more efficacious therapeutically than CY. (17 Refs)

4. CROSS RESISTANCE AND CELLULAR UPTAKE OF 4'-O-METHYLDOXORUBICIN IN EXPERIMENTAL TUMORS WITH ACQUIRED RESISTANCE TO DOXORUBICIN.

Di Marco A, Skovsgaard T, Casazza AM, Pratesi G, Nissen NI, Dano K
(c/o Dano) Lab. Tumor Biology, Univ. Copenhagen, Frederik V's Vej 11, DK-2100 Copenhagen, Denmark
Cancer Chemother Pharmacol; 7(1):15-20 1981

Activity of 4-O-methyldoxorubicin (MDR) against lines of Ehrlich and P388 ascites tumors in which resistance to doxorubicin (DOX) was acquired after treatment with the drug was investigated. Results of in vitro studies of cellular uptake of MDR are reported. At their optimal doses, both MDR and DOX achieved significant and pronounced prolongation of median survival time of mice inoculated with wild-type P388 leukemia cells. No differences between the drugs were noted. When given at the optimal dose for inhibiting wild type P388 cells, both drugs had only a slight effect on the survival of mice inoculated with the DOX-resistant subline, P388/DX+. At drug doses approaching the LD10 the antitumor activity of MDR was comparable to that of DOX in wild type Ehrlich ascites tumor-inoculated mice, whereas no activity could be demonstrated against a similar tumor line selected for resistance to DOX. This line was thus cross-resistant to MDR. Inhibition of energy metabolism increased the steady-state uptake of MDR in resistant Ehrlich ascites tumor cells. This uptake was decreased again by restoration of energy metabolism. Thus, there is probably increased extrusion of MDR from DOX-resistant cells. (8 Refs)

ANTITUMOR AGENT EFFICACY IN VITRO

5. THE ANTITUMOR EFFECTS OF ANTHRACYCLINES. II. THE STEREOSPECIFICITY OF THE CARBOMETHOXY GROUP AT POSITION 10 OF THE CLASS II ANTHRACYCLINE MOLECULE.

DuVernay VH, Eubanks D, Perales R, Prestayko AW, Crooke ST
Bristol-Baylor Lab., Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030
Mol Pharmacol; 21(1):196-203 1982

The effects of marcellomycin (MCM), musettamycin (MSM), and their respective position 10 epimers mimimycin (MIMI) and collinemycin (CLM) on nucleic acid synthesis inhibition in whole Novikoff hepatoma ascites cells, on cytotoxicity in vitro (colony survival), and on antitumor activities in mouse L-1210 leukemia cells were examined. Binding of the compounds to calf thymus and salmon sperm DNA was studied. Epimerization of the carboxymethyl group at position 10 in the MCM and MSM molecules causes a significant loss of ability to inhibit DNA and RNA synthesis; the effect was more pronounced in the analogues. The same epimerization caused a loss of cytoxicity of MCM and MSM and a 4 to 32-fold loss of antitumor potency in the mouse L 1210 system. These studies confirm the observation that the principal intracellular target of class II anthracyclines is DNA and that variation in DNA binding causes variation in in vitro and in vivo activities. (30 Refs)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

6. BIOCHEMICAL INTERACTIONS BETWEEN N-(PHOSPHONACETYL)-L-ASPARTATE AND 5-FLUOROURACIL.

Liang CM, Donehower RC, Chabner BA
Clinical Pharmacology Branch, Div. Cancer Treatment, NCI, Bethesda, MD, 20205
Mol Pharmacol; 21(1):224-230 1982

Incubation of Sarcoma 180 cell cytosol with 5,10-CH2-H4folate and (6-3H)5-fluorodeoxyuridylate (FdUMP) yielded a ternary complex containing (6-3H)FdUMP. The complex could be separated from free (6-3H)FdUMP by addition of albumin-coated charcoal, thus allowing quantitation of FdUMP-binding sites in cytosol. In cells treated with 5-fluorouracil (FU: 3-300 uM), free thymidylate synthetase-binding sites, measured by (6-3H)FdUMP binding were diminished. The cytosol from cells pretreated with N-(phosphonacetyl)-L-aspartate (PALA: 100 uM for 12-18 hr) formed no more ternary complexes than control cells, thus not affecting the number of thymidylate synthetase sites. Yet PALA pretreatment augmented inhibition of the enzyme. FU caused a greater inhibition in the PALA-pretreated cells than in control cells. The potentiating effect required a minimum incubation time of 12 hr. PALA evidently prevented the accumulation of d UMP and enhanced the formation of FdUMP, thus potentiating the formation of the L-aspartate transcarbamylase:folate complex. Using a 12-18 hr delay in the chemotherapy sequence of PALA + FU may be important. (30 Refs)

7. EFFECT OF CAFFEINE ON CELL KILLING, MUTATION INDUCTION, DNA REPAIR, AND DNA SYNTHESIS AFTER TREATMENT WITH ETHYL-NITROSOUREA.

Goth-Goldstein R, Painter RB
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Carcinogenesis; 2(12):1267-1271 1981

The effect of caffeine on cell killing, mutation induction, DNA repair, and inhibition of DNA synthesis was investigated in a clonal derivative of M3-1 Chinese hamster cells after treatment with N-ethyl-N-nitrosourea (ENU). Caffeine enhanced cell killing but had no effect on the mutation frequency/ viable cells for the two genetic markers, 6-thioguanine resistance and ouabain resistance. The removal of ethylated purine bases from DNA was as follows: most of the 3-ethyladenine was lost in 20 hr (greater than 85%) and approx 45% of the 7-ethylguanine was lost in 45 hr, whereas 75-93% of the O6-ethylguanine was still present at this time. Caffeine did not seen to influence these rates significantly. The ENU-induced inhibition of DNA synthesis was reversed by caffeine. It is concluded that the potentiation of ENU-induced cell killing by caffeine is caused by the increased frequency of DNA replication past damaged sites in parental DNA. (Author abstract) (25 Refs)

8. ENHANCEMENT OF METHOTREXATE ANTI-CANCER THERAPY BY ALTERATION OF METHYL GROUP NUTRITION IN MICE BEARING L1210 (MEETING ABSTRACT).

Nixon PF

Department of Biochemistry, University of Queensland, St. Lucia, Queensland 40, Australia

Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

This study is to determine whether the efficacy and safety of Methotrexate (MTX) can be enhanced by two measures, either separately or together, namely, use of 5-methyltetradhydrofolate (MF, the normal plasma folate) for 'rescue' and administration of methionine in BDF1 mice bearing L1210 lymphosarcoma. In these preliminary studies 200 L1210 cells were implanted sc, MTX administered sc, 54 hr later and any 'rescue' administered 15 hr later again. MF or Leucovorin (CF) were given sc at 100 mg/kg. Methionine was injected ip at 5 or 25 mg/mouse. MTX doses were 0, 63, 125, 250 or 500 mg/kg. Mice were scored for survival and tumors. Without therapy, mice died from tumors at approximately 15 days whereas toxic deaths were before day 12. In 'rescue' regimens, survival rates after MF were equivalent to those after CF. To test if MF would selectively rescue normal tissues rather than cancer tissues, MF were administered simultaneously with MTX; survival rates were identical to no therapy controls, inferior to use of MTX alone. In 'rescue' regimens, the administration of methionine simultaneously with the MF or CF enhanced efficacy without affecting toxicity. When MTX was administered without MF or CF, the administration of methionine had little effect. (no Refs)

9. COMBINED EFFECTS OF 5-FLUOROURACIL (5FU) AND 2ALPHA DIMETHYLDEHYDROTESTOSTERONE PROPIONATE (2 ALPHA-MDTP) ON MCF-7 HUMAN BREAST CANCER CELLS IN CULTURE (MEETING ABSTRACT).

Fujita H, Teller MN, Stock CC

Division of Chemotherapy, Keio University School of Medicine, Tokyo, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

In vivo, the combination of 5-fluorouracil and 2 alpha dimethyldehydrotestosterone propionate treatment showed at least an additive effect on dimethylbenzanthracene (DMBA)-induced rat mammary tumors. To examine the evaluation of combined effects of 5 FU and 2 alpha-MDTP on MCF-7 human breast cancer cells, measurements were made on the inhibitory effects on cell proliferation and of the incorporation of 14C-thymidine, 14C-uridine and 14C-leucine into cellular DNA, RNA and protein. Combination of 5 FU and 2 alpha MDTP in concentrations tested gave enhanced inhibition of cell proliferation and of the incorporation of the precursors into cellular macromolecular substances as compared with treatment by each agent. This enhanced effect is additive. (no Refs)

10. ENHANCEMENT OF METHOTREXATE CYTOTOXICITY 'IN VITRO' BY SODIUM BUTYRATE (MEETING ABSTRACT).

Lokiec F, Poirier O, Marty M, Larsen CJ, Najean Y
Hopital St. Louis, 75010 Paris, France
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

In our experiments we studied the effects of sodium butyrate, which modifies cell membrane structure by a non completely elucidated mechanism, on a murine leukemic cell line: L 5178Y. First, we determined the minimal sodium butyrate concentration which does not influence cellular growth as that it will not interfere with Methotrexate (MTX) activity. The concentration chosen was 0.5 x 10-3M. Secondly cells were incubated for 24 hr with increasing MTX concentrations: 0.5, 1, 2, 5, 10 and 20 x 10-8M. If 100% is attributed to the cellular growth of cells which did not receive MTX, we obtained for each MTX concentrations: 82 plus or minus 23%, 80 plus or minus 11%, 70 plus or minus 13%, 58 plus or minus 4%, 43 plus or minus 3% and 27 plus or minus 1% respectively. Third, when L 5178Y cells were preincubated for 24 hr in a medium containing 0.5 x 10(-3) M sodium butyrate, then washed and incubated for another 24 hr with the MTX concentrations given above, the cellular growth was: 95 plus or minus 12%, 90 plus or minus 4%, 77 plus or minus 6%, 43 plus or minus 7% and 43 plus or minus 3% respectively, compared to that (100%) of control cells which received only sodium butyrate. In a last experiment, cells were preincubated for 24 hr in a medium containing 0.5 x 10(-3) M sodium Butyrate, then brought into contact for another 24 hr with MTX without previous washing. In this experiment the cellular growth in the presence of MTX was: 92 plus or minus 15%, 69 plus or minus 22%, 38 plus or minus 4%, 26 plus or minus 4%, 26 plus or minus 1% and 25 plus or minus 0.1% respectively. (no Refs)

11. PROLIFERATIVE-DEPENDENT CYTOTOXICITY OF CYCLOPHOSPHAMIDE ON HUMAN TUMOR XENOGRAFTS IN ATHYMIC NUDE MICE (MEETING ABSTRACT).

Mattern J, Jaeger S, Wayss K, Volm M
Department of Pathology, German Cancer Research Center, Heidelberg, W. Germany
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

The effect of cyclophosphamide, given as a single ip injection (240 mg/kg) on various fast growing human tumor lines from different origin (lung, ovary, colon) transplanted and passes serially in athymic nude mice, were studied. MNRI-nude mice (6-9 wk old) were used, treatment being started when tumor diameter reached 8-10 mm. The delay of tumor growth was used as endpoint in vivo. Cyclophosphamide showed significant activity against all tumors studied. However, there was a considerable range of sensitivity of the different lines to the agent studied. When the effect of the drug (growth delay) is correlated with the growth rate (vol doubling time) of the untreated xenografts, a relationship becomes apparent. The faster a tumor is growing the more pronounced is the inhibitory effect of cyclophosphamide on growth, independent of tumor type or histology. The results show that if tumors are treated under standarized conditions (ie the same tumor size at the beginning of the treatment, same location of tumor implantation, same age and strain of the animals, same route of application of the medicament) growth rate is a factor of decisive importance for the sensitivity of a tumor to cyclophosphamide. (no Refs)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

12. HAEMOPOIETIC STEM CELLS: POSSIBILITY OF TOXIC EFFECTS OF 5-FLUOROURACIL ON SPLEEN COLONY FORMATION.

Rosendaal M, Dixon R, Panayi M
Dept. Anatomy and Embryology, Univ. Coll. London, Grower St., London WC1E 6BT, England
Blood Cells; 7(3):561-574 1981

Possible toxic effects of 5-fluorouracil (5-FU) on spleen colony formation were tested using bone marrow cells collected from male BIOC F1 hybrid mice treated with 5-FU (5-FUBM). A single dose of 5-FUBM (150 mg/kg/body wt) showed that the number of colony forming units (CFU) rises steeply with the passage of time after such a graft. Normal bone marrow cells did not have such an effect. Four p ossible sources of extra colonies were investigated. Extra colonies (EC) might arise by reseeding of CFU formed in the marrow or the spleen; EC might arise from CFU which settle in spleen but require a variable time until they can start to cycle, or EC might arise after a variable time as CFU repair the damage done by 5-FU. CFU which eventually form spleen colonies are in the spleens of recipients 24 hr after the graft. EC do not arise by reseeding of CFU formed in the spleens of recipients. EC forming index was measured 1, 2, and 3 days after administration of 5-FU. The number of CFU/femur was measured over the same period. Mice with very small quantities of 5-FUBM must be reconstituted to enable counting of colonies at long intervals after grafting to find out the true extent of kill. EC may arise after CFU repair the damage done by 5-FU. (15 Refs)

13. ADRIAMYCIN-INDUCED NEPHROTIC SYNDROME IN RATS: SEQUENCE OF PATHOLOGIC EVENTS.

Bertani T, Poggi A, Pozzoni R, Delaini F, Sacchi G, Thoua Y, Mecca G, Remuzzi G, Donati MB
Div. Nephrology, Ospedali Riuniti, Bergamo, Italy
Lab Invest; 46(1):16-23 1982

Adriamycin has been suspected of causing experimental nephrotoxicity. We report here that adriamycin induces a nephrotic syndrome in rats, proteinuria beginning 4 to 5 days after a single iv injection (7.5 mg per kg of body wt). The full expression of the syndrome develops 13 to 15 days later. Minimal alterations at light microscopy, negative immunofluorescence, and only some focal 'fusion' of foot processes can be observed by electron microscopy in the early phase after injection (28 hr). AT 13 days, loss of foot process architecture, and replacement by flattened epithelial cytoplasm, was invariably found. These ultrastructural findings became extensive at 28 days follow-up. Colloidal iron staining of kidney biopsies revealed loss of glomerular polyanions as early as 3 hr and very marked loss at 28 hr after adriamycin injection. Polyanions were totally absent at 13 days and were still undetectable at 28 days. Thus, the loss of polyanionic charges associated with the sialic acid coat precedes the ultrastructural changes and the onset of proteinuria. These changes appeared similar to those reported in rats treated with daunomycin or puromycin aminonucleoside. The present study supports in a different animal model the concept that both morphologic changes and proteinuria are the consequence of a common primary event that is the loss of glomerular fixed negative charges. (Author abstract) (22 Refs)

14. BEHAVIORAL INVESTIGATION OF NEUROTOXICITY: THE EFFECTS OF COLCHICINE, LUMICOLCHICINE AND VINCRISTINE SULFATE ON GOLDFISH OPTIC NERVE DEGENERATION.

Davis RE, Benloucif S
Neuroscience Lab., Univ. Michigan, Ann Arbor, MI, 48109
Neurotoxicology; 2(3):419-430 1981

Recovery of vision following optic nerve crush was measured in goldfish following the ip administration during recovery of colchicine, lumicolchicine, and vincristine sulfate. A behavioral protocol was used to determine toxic effects of the alkaloid neurotoxins on regenerating nerve fibers. Regeneration was inhibited by colchicine and vincristine sulfate but not by lumicolchicine. The results indicated that a behavioral protocol can be used to estimate relative neurotoxicity of agents which impair neuronal development in vivo. (19 Refs)

15. RESIDUAL DAMAGE IN HEMATOPOIETIC CELLS FOLLOWING A SINGLE DOSE ADMINISTRATION OF METHYL NITROSOUREA (MEETING ABSTRACT).

Inoue T
Department of Pathology, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

To evaluate residual damage from leukemogenic agents, capabilities of proliferation in hematopoietic stem cells (CFUs) in mice treated iv with a single leukemogenic dose (50 mg/kg body wt) of methyl nitrosourea (MNU) were examined by means of spleen colony assay, 3H-thymidine cytocide, 125 iodo-deoxyuridine incorporation into spleen and bone marrow in fatally irradiated mice transfused with 4.5 x 10(6) bone marrow cells from treated mice. Mice given MNU and kept for 3 wk were compared with a group, which had been kept for 3 days after the administration of MNU, for acute toxicity. No significant changes were observed between control and MNU-treated mice kept for 3 wk, in total bone marrow cells, number of CFUs per femur or unit number of cells, and thymidine cytocide rate of the CFUs-pool. Significant change, however, was observed in the proliferation capability of CFUs. (no Refs)

16. THE EFFECT OF DIANHYDRODULCITE AND DIACETYL-DIANHYDRODULCITE ON HUMAN BONE-MARROW COLONY FORMING CELLS IN CULTURE (CFUC) (MEETING ABSTRACT).

Ujj G, Kovacs P, Kiss A, Mikita J, Rak K, Hernadi F
2nd Department of Medicine, University Medical School, Debrecen, Hungary
Ninth Congress of the Haematological Society, October 1-3, 1981, Debrecen, Hungary. The Society 175 pp., 1981.

The effect of two cytostatic hexit derivates (dianhydrodulcite (DAD) and diacetyl-dianhydrodulcite (diac-DAD) was studied in human bone-marrow colony forming cells in culture (CFUc). The survival of CFUc after a 3 and 5 ug/ml DAD treatment was 71 and 34 per cent, respectively, while the survival time after 20 and 30 ug/ml of diac-DAD treatment was 69 and 33 per cent, respectively. The damage of human CFUc was significantly less at both concentrations of both cytostatics than the damage of CFUc of mice treated in the same way. The results indicate that no direct conclusions on the damage of the human hemopoiesis caused by cytostatics can be drawn from laboratory animal experiments. (no Refs)

17. ANTITUMORAL AND TOXIC PROPERTIES OF PHOSPHOLIPID VESICLES CONTAINING CIS-DIAMMINEDICHLOROPLATINUM.

Muzia GI, Barsukov LI, Gor'kova NP, Sorokina IB, Piruzian LA, Bergel'son LD, Moshkovskii IuSh
M. M. Shemiakin Inst. Bioorganic Chemistry, Moscow, USSR
Biull Eksp Biol Med; 91(11):590-593 1981

Antineoplastic activity and toxicity of cisplatin (CP) administered in phospholipid vesicles were studied in random-bred albino mice with sc transplanted Crocker's sarcoma. Animals received single iv administration of cisplatin 48 hr after tumor transplantation. Animals in Group 1 received 10 mg/kg of CP in physiological soln, Group 2 received 10 mg/kg of CP in liposomes, and Group 3 received 20 mg/kg of CP in liposomes. CP in liposomes caused significant inhibition of tumor growth (25% in Group 2 and 39% in Group 3, compared with 75% in Group 1). Liposomes reduced toxicity of CP measured by the changes of spleen wt and the decrease of WBC count. CP concentration in in the liver and in the spleen after administration in the liposomes was significantly lower than those after administration in the physiological soln, while CP content in the kidneys was significantly lower after liposomes administration. These findings indicate that liposomes permit administration of higher doses of CP. (11 Refs) (In RUS)

18. DIFFERENTIAL SURVIVAL OF CELL SUBPOPULATIONS IN SPHEROIDS AFTER TREATMENT WITH BLEOMYCIN.

Toburen D
Inst. Radiobiology, Univ. Munster, Hittorftstr. 17, D-4400 Munster, W. Germany
J Cancer Res Clin Oncol; 102(2):189-193 1981

The cytotoxic effect of bleomycin (BLM) on Chinese hamster V79-cells grown as spheroids is compared to that on monolayer cultures in exponential vs plateau phase of growth. Cells treated as intact spheroids with BLM (50 ug/ml for 1 hr) are more sensitive than monolayer cultures. Cell subpopulations derived from different zones of the spheroids survive BLM-treatment to different degrees: When treated as single cells in suspension, the formerly 'outer' cells are less affected than the 'inner' cells. Within intact spheroids, however, progressive cellular resistance with increasing distance from the outer rim is found. (Author abstract) (17 Refs)

19. INHIBITION OF CARDIAC GUANYLATE CYCLASE BY DOXORUBICIN AND SOME OF ITS ANALOGS: POSSIBLE RELATIONSHIP TO CARDIOTOXICITY.

Lehotay DC, Levey BA, Rogerson BJ, Levey GS
930 Scaife Hall, Univ. Pittsburgh, Sch. of Medicine, Pittsburgh, PA, 15261
Cancer Treat Rep; 66(2):311-316 1982

The anthracycline antibiotic doxorubicin induces a variety of cardiotoxic effects. We have recently demonstrated that this drug also causes a selective inhibition of rat and human cardiac guanylate cyclase activity in vitro. In the present study, we examined the effect of 30 analogs of doxorubicin on cardiac guanylate cyclase activity. Structural modifications of these anthracycline anti biotics were found to alter their effect on rat cardiac guanylate cyclase activity. N-substitutions on the sugar moiety eliminated the inhibitory action observed with the parent compound. Long-chain hydrocarbon substitutions in place of the methylketone side chain had a similar effect. Removal or substitution of the C-4 methoxy group had little or no effect on the ability of these compounds to modify guanylate cyclase activity. Substitutions of the C-9 side chain by a hydrazone derivative resulted in compounds that stimulated the enzyme. All of the anthracenedione derivatives were inhibitory. A comparison of the inhibitory effect of some of these anthracycline derivatives on in vitro cardiac guanylate cyclase activity with their cardiotoxic potency suggests a possible relationship between these two parameters. (Author abstract) (43 Refs)

20. ASSESSMENT OF THE TERATOGENIC POTENTIAL OF ACROLEIN AND CYCLOPHOSPHAMIDE IN A RAT EMBRYO CULTURE SYSTEM.

Schmid BP, Goulding E, Kitchin K, Sanyal MK
Preclinical Res., Pharmaceutical Div., Sandoz Ltd., CH-4002 Basle, Switzerland
Toxicology; 22(3):235-243 1981

Relative embryotoxicity of acrolein (AC) was tested with the rat postimplantation embryo culture system and the effects were compared with those due to an intermediate metabolite, cyclophosphamide (CPA). Effects of AC and CPA on the development of 10.5 day-old rat conceptuses in vitro are presented. Findings indicate that AC is lethal to embryos within a narrow dose-range, but has no teratogenic potential. Results also demonstrate that the postimplantation embryo culture system can discriminate between embryolethal and teratogenic effects and that whole embryos in culture can respond to teratogens in a manner similar to embryos exposed in vivo. (35 Refs)

21. THE PREVENTION OF CYCLOPHOSPHAMIDE-INDUCED CYSTITIS IN MICE BY DISULFIRAM.

Hacker MP, Newman RA, Ershler WB
Dept. Pharmacology, Univ. Vermont Sch. Medicine, Burlington, VT, 05405
Res Commun Chem Pathol Pharmacol; 35(1):145-154 1982

Cyclophosphamide administered intraperitoneally to mice at a dose of 100 mg/kg caused a dose related increase in urinary bladder wt within 48 hr of treatment. Disulfiram effectively prevented cyclophosphamide-induced increase in bladder wt when disulfiram was administered by either the oral or intraperitoneal route. Disulfiram (125 mg/kg) was most effective when given within 1 hr of cyclophosphamide treatment. These results suggest that disulfiram, unlike other putative protectants, is effective when administered orally. (Author abstract) (16 Refs)

22. COMPARATIVE TOXICITY OF CHEMOTHERAPY FOLLOWING PARTIAL HEPATECTOMY.

Grosfeld JL, Weber TR, Baehner rL, Hays DM, Vos A, Filler RM
Dept. Surgery, J.W. Riley Hosp. for Children (K-21), 1100 West Michigan St., Ind ianapolis, IN, 46223
J Pediatr Surg; 16(6):950-954 1981

Effects of commonly employed chemotherapeutic agents on regenerating liver was studied in 200 Sprague Dawley rats. After 70% hepatectomy, animals were divided into four groups: Group I consisted of untreated controls, Group II received actinomycin D (AMD) at 150 ug/kg iv, Group III received vincristine (VCR) at 0.2 mg/kg iv, and Group IV received adriamycin (ADR) at 30 mg/square meter iv. Thymidine incorporation into DNA and thymidine degradation to carbon dioxide were measured in liver slices. Peak DNA levels (8.2 x 10(3) cpm) and lowest CO2 levels were seen at 24 hr in control animals. Group III animals had values for both parameters which were similar to those in controls. Thymidine incorporation into DNA in Group IV (ADR) animals was 5.1 x 10(3) cpm; incorporation was lowest in Group II animals (AMD), at 3.78 x 10(3) cpm. Liver wt in ADR and AMD-treated animals was significantly lower than in controls or VCR-treated animals. Results indicate that while AMD and ADR severely inhibit DNA synthesis in regenerating liver, VCR is relatively benign. (11 Refs)

23. COMPENSATORY POTENTIALS OF HEMATOPOIETIC TISSUE IN ANIMALS DURING RECOVERY OF MORPHOLOGICAL BLOOD COMPOSITION AFTER CARMINOMYCIN ADMINISTRATION.

Novitskii VV, Gol'dberg ED, An'shakova NA
Dept. Physiopathology, Medical Inst., Tomsk, USSR
Antibiotiki; 26(12):901-906 1981

Effect of antineoplastic antibiotic carminomycin (CM: 0.3 mg/kg, ip, qod) on the hematopoietic tissue was studied in random-bred albino rats. Morphological composition and functional state of the bone marrow and peripheral blood were evaluated on day 30 after completion of CM administration. Adrenaline and hydrocortisone tests showed depletion of the granulocyte pool. (10 Refs) (In RUS)

24. RELATIONSHIP OF IRON METABOLISM TO TUMOR CELL TOXICITY OF STABLE GALLIUM SALTS.

Rasey JS, Nelson NJ, Larson SM
Dept. Radiation Oncology, Univ. Washington, Seattle, WA
Int J Nucl Med Biol; 8(4):303-313 1981

The antitumor properties of citrated gallium nitrate (NSC 15200) have been tested using the EMT-6/UW mouse sarcoma growing in vitro or in vivo. This tumor system has been used in both growth forms in our studies which led to the transferrin receptor hypothesis of the mechanism of uptake of tracer levels of gallium-67 citrate. Gallium nitrate is both cytostatic and lethal in vitro with some growth inhibition occurring after chronic exposure to low doses (10 ug per ml) which kill essentially no cells. Cell kill and growth inhibition were both observed if cells were exposed for longer times at higher doses. The effects of gallium nitrate were enhanced by the addition of human transferrin to the culture medium. The enhanced toxicity was consistent with, and proportional to, increased gallium uptake in the presence o f transferrin. The addition of ferric citrate greatly reduced the toxic effect of the gallium salt. The enhancing effect of transferrin and protective action of ferric citrate are consistent with our studies of the effect of these two agents on concentration of tracer levels of the tumor-imaging radiopharmaceutical, carrier-free gallium-67 citrate. Tumors in vivo were largely resistant to 10 daily doses of 90 mg kg-1 of gallium nitrate. Ga may mimic Fe in some aspects of cell metabolism. Competition between the two metals occurs at the initial uptake step (binding to transferrin) and possibly to a lesser extent at other points in cellular incorporation and deposition. Iron has been implicated as a regulatory factor in cell growth and may be essential for cell proliferation. The toxicity of stable gallium is interpreted in the context of similarities of metabolism of the two metals. (Author abstract) (20 Refs)

25. CONTRASTS BETWEEN THE RESPONSE OF THE MOUSE HAEMOPOIETIC SYSTEM TO 5-FLUOROURACIL AND IRRADIATION.

Dixon R, Rosendaal M

Dept. Anatomy and Embryology, Univ. Coll. London, Grower St., London WC1E 6BT, England

Blood Cells; 7(3):575-587 1981

Responses of the mouse hemopoietic system to 5-fluorouracil (5-FU), shielded-limb irradiation, and total-body irradiation plus bone marrow injection, and to a dose of 5-FU given 10 wk subsequent to each of these treatments, were studied. After 5-FU the numbers of spleen colony forming units (CFU) rose rapidly above normal levels 11 days after treatment, but the numbers of granulocyte-macrophage colony forming cells (GM-CFC) increased more slowly and remained subnormal. GM-CFC number reached normal 3-4 wk after partial-body irradiation or irradiation/reconstitution, although the CFU number rose slowly and did not reach pre-treatment levels. Two explanations for the difference are discussed; irradiation damages the hematopoietic environment in a way which prohibits fast proliferation of CFU, and 5-FU inhibits the differentiation of CFU into committed precursors. Two possible causes of artifact in CFU assays were investigated and corrected. The seeding efficiency of CFU, which varies according to cycling status, was adjusted by deducing cycling status from rate of change of CFU number. The second correction was for delayed colony formation by CFU after treatment with 5-FU. The response to a subsequent dose of 5-FU was the same in all groups, indicating that radiation damage to the stroma is either non-existent after 850 rad, or is repaired within 10 wk, or is irrelevant to the recovery from 5-FU. No difference was seen between the responses to partial-body irradiation and to transplantation. (25 Refs)

26. COMPARATIVE CARDIAC AND RENAL TOXICITY OF DAUNORUBICIN IN THE RAT AND RABBIT.

Deprez-DeCampeneere D, Jaenke R, Trouet A

(c/o Jaenke) Dept. Pathology, Coll. Veterinary Medicine and Biomedical Sciences, Colorado State Univ., Ft. Collins, CO, 80523

Cancer Treat Rep; 66(2):395-397 1982

A direct comparison of the cardiac and extracardiac effects of repeated daunorubicin administration in the rat and rabbit demonstrated a basic similarity in the cardiac myocyte response. The rat, however, appears to develop a more severe drug-related nephropathy, resulting in widespread soft tissue mineralization that includes vessels and the myocardium. These findings suggest that the severity and development of acute and chronic anthracycline-induced cardiac lesions may, in the rat, be related or dependent, in part, on concomitant nephrotoxicity. (Author abstract) (10 Refs)

PHARMACOKINETICS OF ANTITUMOR AGENTS

27. TISSUE DISTRIBUTION OF DOXORUBICIN AND DOXORUBICINOL IN RATS RECEIVING MULTIPLE DOSES OF DOXORUBICIN.

Peters JH, Gordon GR, Kashiwase D, Acton EM
Life Sciences Div., SRI International, Menlo Park, CA, 94025
Cancer Chemother Pharmacol; 7(1):65-69 1981

Levels of doxorubicin (DXR) and doxorubicinol (DXR-OL) in plasma and various tissues were measured in female Sprague-Dawley rats receiving single or multiple doses of DXR. Eighteen rats were given 1, 9, or 24 doses of 1.0 mg DXR/kg. Ten rats received one or eight doses of 4.0 mg/kg. Controls received only vehicle. Rats from each group were killed 1, 3, and 24 hr after the last dose of DXR. With a dose rate of 1.0 mg/kg, plasma levels after 1 hr, in ug/g protein, were 0.086 after 1 dose, 0.23 after 9 doses, and 0.34 after 24 doses, indicating a progressive build-up after multiple treatments. After 3 hr plasma levels of DXR were 0.11 with 1 dose, 0.092 with 9 doses, and 0.050 with 24 doses, indicating a progressive decrease. Liver tissue showed a rapid build-up of DXR to levels much higher than in plasma. These levels did not increase with successive doses. DXR accumulated slowly in the heart; after multiple doses DXR in the heart exceeded that in the liver. Skeletal muscle accumulated DXR in a dose-related manner at absolute levels approx 10% of those in the heart. Tissue samples contained DXR-OL at levels less than 4% of DXR levels; plasma contained DXR-OL at levels up to 85% of plasma DXR levels. (20 Refs)

28. PHARMACOKINETICS OF LIPOSOME ENTRAPPED BLEOMYCIN AND ITS ENHANCING ANTICANCER EFFECT (MEETING ABSTRACT).

Hata M, Tachibana M, Hagiwara M, Deguchi N, Tazaki H
Department of Urology, Keio University School of Medicine, Tokyo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The tissue distribution of bleomycin and its anticancer effects in tumor bearing nude mice were analyzed with special regard to comparison between free and liposome entrapped bleomycin. More accumulation of liposome entrapped bleomycin in the reticuloendothelial system (RES) was demonstrated while no significant increase in the tumor tissue. Stronger inhibition on the growth of human renal cancer cell line (KU-2) by liposome entrapped bleomycin was found as well as that of the animal experiments. This enhanced activity was explained by slow release rather than providing selective delivery of the drug to the tumor cells. (no Refs)

29. DOES ADRIAMYCIN UNDERGO AN ENTEROHEPATIC CIRCULATION?

Tavoloni N, Guarino AM
Polly Annenberg Levee Hamatology Center, City Univ. New York, Mt. Sinai Sch. Medicine, 1 Gustave L. Levy Place, New York, NY, 10029
Proc Soc Exp Biol Med; 169(1):41-46 1982

Absorption of adriamycin (ADR) from the small intestine of anesthetized male Sprague-Dawley rats with biliary and urinary fistulae was investigated. Rats were intraduodenally perfused with bile from bile duct-cannulated rats which had been injected iv with 20 mg/kg [14C]ADR. Approx 10% of the total drug equivalents eliminated through the bile over a 6-hr period were reabsorbed from the lumen of the small intestine; this amount roughly represents 3% of the iv administered ADR. (12 Refs)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

30. ENHANCED ANTITUMOR PROPERTIES OF 3'-(4-MORPHOLINYL) AND 3'-(4-METHOXY-1-PIPERIDINYL) DERIVATIVES OF 3'-DEAMINODAUNORUBICIN.

Mosher CW, Wu HY, Fujiwara AN, Acton EM
Bio-Organic Chemistry Lab., Life Sciences Div., SRI International, Menlo Park, CA, 94025
J Med Chem; 25(1):18-24 1982

Reductive N,N-dialkylation of daunorubicin with 2,2'-oxydiacetaldehyde and NaBH3CN occurred in two steps without interruption and with cyclization to form 3'-(4-morpholonyl)-3'-deaminodaunorubicin. This derivative retained the antitumor efficacy of doxorubicin against mouse leukemia P388 but at one-fortieth the dose; hence, it is the most potent anthracycline analogue synthesized so far. The 4-methoxy-1-piperidinyl derivative, similarly prepared with 3-methoxygluytaraldehyde, showed improved efficacy against p388, though at normal doses. Results with a series of analogues indicate that incorporation of the N in the new ring and the presence of an ether O at the 4-position are critical for enhanced activity. (Author abstract) (19 Refs)

31. ADRIAMYCIN ANALOGUES. PREPARATION AND ANTITUMOR EVALUATION OF 7-O-(BETA-D-GLUCOSAMINYL)DAUNOMYCINONE AND 7-O-(BETA-D-GLUCOSAMINYL)ADRIAMYCINONE AND THEIR N-TRIFLUOROACETYL DERIVATIVES.

Israel M, Murray RJ
Div. Pharmacology, Sidney Farber Cancer Inst., Boston, MA, 02115
J Med Chem; 25(1):24-28 1982

The title compounds were prepared by Koenigs-Knorr condensation of 3,4,6-tri-O-acetyl-2-deoxy-2[(trifluoroacetyl)amino] alpha-D-glucopyranosyl bromide with daunomycinone or a side-chain protected adriamycinone, followed by selective hydrolysis of blocking groups. Despite poor complexation with DNA and weak growth-inhibitory properties in vitro, the glucos aminyl analogues of the antitumor antibiotics daunorubicin and adriamycin, at their optimal (highest nontoxic) doses, exhibited antileukemic activity equivalent to that of adriamycin against a usually drug-refractory mouse leukemia model system (L1210) in vivo. These findings, together with other data from these laboratories, continue to support the hypothesis that the mechanism of action of adriamycin and related agents cannot be due exclusively to DNA binding, as has earlier been believed. (Author abstract) (30 Refs)

32. ADRIAMYCIN ANALOGUES. NOVEL ANOMERIC RIBOFURANOSIDE ANALOGUES OF DAUNORUBICIN.

Israel M, Airey JE, Murray RJ, Gillard JW
Div. Pharmacology, Sidney Farber Cancer Inst., Boston, MA, 02115
J Med Chem; 25(1):28-31 1982

The synthesis, cell growth-inhibitory activity, in vivo antileukemic activity, and extent of DNA binding of the alpha- and beta-anomeric 7-O-(3-amino-3,5-dideoxy-D-ribofuranosyl)daunomycinones and their trifluoroacetamides are described. These compounds are unique in that they are the first reported furanoside analogues of the antitumor antibiotics daunorubicin and adriamycin. Continuing analysis of structure-activity relationships amongst natural and semisynthetic anthracyclines fails to reveal a predictable relationship between in vivo antitumor activity and the in vitro properties of DNA complexation and cell growth inhibition. (Author abstract) (27 Refs)

33. SYNTHESIS AND ANTINEOPLASTIC ACTIVITY OF THE 13-TERT-BUTOXYCARBONYLHYDRAZONE DERIVATIVE OF RUBOMYCIN.

Povarov LS, Gol'dberg LE, Bazhanov VS, Olsuf'eva EN, Averbukh LA, Filippos'iants ST

All-Union Res. Inst. Screening for New Antibiotics, Moscow, USSR
Antibiotiki; 26(11):813-816 1981

Toxicity and antitumor activity of the 13-tert-butoxycarbonylhydrazone (BOCH) derivative of rubomycin (RM) were studied in random-bred mice bearing lymphosarcoma LIO-1, Harding-Passey melanoma, leukemia L-1210, or leukemia P-388. The BOCH-RM was less toxic than RM and was 2.7x less active against lymphosarcoma LIO-1 than the RM. At 19 and 28.5 mg/kg, the BOCH-RM provided 62% and 75% inhibition, respectively, of the Harding-Passey melanoma. The derivative was ineffective against the leukemia L-1210 and was significantly less effective than RM against the leukemia P-388. (6 Refs) (In RUS)

34. ANTITUMOR ACTIVITY OF BIOSYNTHETIC TALLYSOMYCIN DERIVATIVES (MEETING ABSTRACT).

Imanishi H, Nishiyama Y, Ohbayashi M, Miyaki T, Kawaguchi H

No affiliation given

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

A series of new biosynthetic derivatives of tallysomycins A and B were prepared by precursor-feeding fermentations. Certain diamines were incorporated into tallysomycins as the term inal amine moiety, affording two classes of biosynthetic derivatives with or without the beta-lysine moiety in the subterminal position. Twenty-one tallysomycin derivatives were screened for antitumor activity against P388 leukemia, sarcoma 180 and B16 melanoma. Tallysomycin S10b, a tallysomycin B derivative having 1,4-diaminobutane as the terminal amine moiety, was selected for further study in view of its favorable therapeutic indices. The antitumor activity of tallysomycin S10b against Lewis lung carcinoma and B16 melanoma was comparable to that of tallysomycin A and about 3 times higher than that of bleomycin. Tallysomycin S10b was more active than tallysomycin A against sarcoma 180 but less active than the latter against leukemia P388. Tallysomycin S10b was less toxic than tallysomycin A in terms of acute and subacute LD50 values. The nephrotoxic potential of tallysomycin S10b in rats was less than that of tallysomycin A. Tallysomycins were found more stable than bleomycin when incubated with murine liver homogenate. (no Refs)

35. ANTITUMOR ACTIVITY OF AN ANTIBIOTIC, IDENTICAL WITH OR CLOSELY RELATED TO XANTHOMYCIN A (MEETING ABSTRACT).

Nishimura T, Tanaka N
University of Tokyo, Tokyo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

In a screening program for tumor-inhibitory antibiotics, we isolated an antibiotic, identical with or closely related to xanthomycin A from a Streptomyces. Since the antitumor activity has not appeared in the literature, we studied the activity. The antibiotic displayed significant therapeutic activity by ip injection against ip-implanted mouse tumors: Ehrlich carcinoma, sarcoma 180 and P388 leukemia. Less therapeutic activity was observed by the ip injection in mice, bearing sc solid tumors of Ehrlich carcinoma and sarcoma 180. No significant activity was found against L1210 leukemia, B16 melanoma and Lewis lung carcinoma. In vitro the antibiotic showed a potent cytotoxicity to human leukemia K562 and mouse lymphoblastoma L5178Y cells. Strand scission of PM2 cccDNA was caused by the drug in the presence of dithiothreitol. (no Refs)

36. MICROBIAL TRANSFORMATION OF SAFRAMYCIN A (SA) AND ANTITUMOR ACTIVITY OF SAFRAMYCIN AR1 (AR1, 25-DIHYDROSAFRAMYCIN A) (MEETING ABSTRACT).

Takahashi K, Kishi K, Mikami Y, Arai T
Chiba University, Chiba, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

In order to obtain SA derivatives which show different antitumor spectra and biological properties, microbial transformation of SA was attempted. AR1 and saframycin AR3 (AR3) are the SA bioconversion products by Rhodococcus amidophilus, of which the structures were determined as 25-dihydrosa framycins A and B. AR1 showed one tenth antimicrobial activity of SA. AR3 proved to be almost inactive on test organisms. ED50's of AR1 and AR3 against L1210 cell culture were found to be 5x10(-3) mcg/ml and greater than 1 mcg/ml, respectively. In spite of lower cytotoxicity of AR1 than that of SA, AR1 showed in vivo activity on L1210 leukemia (ILS: 156%) almost equivalent to with SA. The above results indicated that saframycin derivatives which possess interesting antitumor characteristics might be obtained by means of microbial transformation. (no Refs)

37. ACTION OF LYCURIM AND PYRAZOFURIN ON HEPATOMA 3924A CELLS IN CULTURE.

Ban J, Olah E, Weber G
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Cancer Treat Rep; 66(2):343-349 1982

The purpose of this study was to test for a possible synergism in the antitumor action of the antimetabolite pyrazofurin (PF) and the alkylating agent lycurin (LY) [1,4-di-(2'-mesyloxy-ethylamino)-1,4-dideoxy-m erythritol dimethylsulfonate] on proliferating and resting rat hepatoma 3924A cells in tissue culture. Earlier studies showed that PF killed hepatoma cells only in the logarithmic phase of growth as determined by colony-forming ability. Now we report that LY killed hepatoma cells in both the exponential and plateau phases. Treatment of cultures in each phase for 1 or 2 hrs resulted in threshold exponential type dose-response curves, yielding Do values of 3 and 1 uM, respectively. LY is a cycle-specific drug, although fluctuations in cell age-dependent survival were also demonstrated. In synchronized cultures, cells were most sensitive to 0.1 uM LY in early G1 phase, but in higher concentration (5 uM), LY killed the cells during the entire cell cycle, especially in G1, early and mid S phases, and M phase. Lycurim and PF given together in their IC50 concentrations (0.016 and 0.085 uM, respectively) yielded synergistic cell kill in 7-day treatment of proliferating cultures. Two-hour treatment of exponentially growing cells with LY and PF at their IC50 concentrations (1 and 20 uM, respectively) also yielded synergistic killing action, but in plateau-phase cells only summation was observed. Synergistic activity of LY and PF in hepatoma 3924A cells was dependent on drug concentration and incubation time. (Author abstract) (24 Refs)

38. COMPARISON OF THE EFFECTS ON CULTURED L1210 LEUKEMIA CELLS OF THE RIBOSYL, 2'-DEOXYRIBOSYL, AND XYLOSYL HOMOLOGS OF TUBERCIDIN AND ADENOSINE ALONE OR IN COMBINATION WITH 2'-DEOXYCOFORMYCIN.

Cass CE, Selner M, Tan TH, Muhs WH, Robins MJ

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Cancer Treat Rep; 66(2):317-326 1982

The biologic effects of a series of sugar-substituted analogs of tubercidin were evaluated and compared with the effects of the homologous series of adenosine analogs in combination with 2'-deoxycoformycin. The greatest cytotoxicity against cultured mouse L1210 leukemia cells was exhibited by tubercidin and by 3'-deoxyadenosine or xylosyladenine in combination with 2'-deoxycoformycin. Somewhat less active were xylotubercidin and the combination of arabinosyladenine (araA) pius 2'-deoxycoformycin. The arabinosyl and 2'- and 3'-deoxyribosyl derivatives of tubercidin were relatively ineffective in their ability to inhibit proliferation of L1210 cells. The major biochemical effects of the most active agents were inhibition of RNA synthesis (3'-deoxyadenosine and xylosyladenine) and depletion of cellular ATP plus general inhibition of macromolecular synthesis (tubercidin). The in vitro activities of xylosyladenine and 3'-deoxyadenosine (in combination with 2'-deoxycoformycin) and xylotubercidin (as a single agent) were greater than or equivalent to that of araA (in combination with 2'-deoxycoformycin). (Author abstract) (22 Refs)

39. NEW ANTITUMOR ANTIBIOTIC DC-14.

Shimizu K, Ohkubo S, Morimoto M, Tomita F

(c/o Tomita) Tokyo Res. Lab., Kyowa Hakko Kogyo Co. Ltd., Machida, Tokyo, Japan

J Antibiot (Tokyo); 35(1):87-89 1982

An actinomycete strain DO-14 (Streptomyces olivaceus) isolated from soil is shown to produce an anthraquinone antibiotic (DC-14) of molecular formula C43H50N2O13. DC-14 inhibited the growth of gram-positive and weakly gram-negative bacteria, and was active against murine sarcoma virus 180 in vivo at doses of 1.5-6.0 mg/kg. Acute toxicity (LD50) of DC-14 ip in mice was about 8 mg/kg. (7 Refs)

40. ACTIVATED N-NITROSOCARBAMATES FOR REGIOSELECTIVE SYNTHESIS OF N-NITROSOUREAS.

Martinez J, Oiry J, Imbach JL, Winternitz F
Equipe de Recherche Associee au CNRS 195, Ecole Nationale Superieure de Chimie de Montpellier, 34075 Montpellier, France
J Med Chem; 25(2):178-182 1982

A practical and convenient method for synthesizing antitumor compounds, N-alkyl-N-nitrosoureas, regioselectively nitrosated on the nitrogen atom bearing the alkyl group is proposed. N-Alkyl-N-nitrosocarbamates are interesting intermediates in these syntheses and yield, by reaction with amino compounds, the regioselectively nitrosated N-alkyl-N-nitrosoureas. As an interesting example, N,N'-bis[(2-chloroethyl)nitrosocarbamoyl]cystamine, a new attractive oncostatic derivative, has been prepared. The cytotoxic activity of these various compounds were tested on L1210 leukemia. (Author abstract) (23 Refs)

41. STUDIES ON PATHOMORPHOLOGY, BIOLOGICAL PROPERTIES, AND SENSITIVITY TO ANTI-TUMOR AGENTS OF THE TRANSPLANTABLE SQUAMOUS CELL CARCINOMA (GS-742) OF MOUSE FORESTOMACH.

Lin B, Dou G, Cui Z, Sun Y, Zhang X, Li Q
Experimental Tumor Lab., Tianjin Medical Coll., Tianjin, People's Republic of China
Zhonghua Zhongliu Zazhi; 3(2):101-105 1981

Murine forestomach carcinoma cell line, GS-742, was originally induced in inbred Jinbai mice by N-methylnitrosourea; this transplantable cell line has been successfully propagated in syngeneic mice for 74 generations over a period of more than 5 yr. Its growth characteristics were stable with a graft survival rate of 100% and with no spontaneous regression; the av host survival time was about 2 mo. Pathomorphologically, this cell line was a typical squamous cell carcinoma with lymph node metastasis resembling human esophageal carcinoma. Electron microscopy showed tonofilaments and desmosomes in the cytoplasm, large intercellular spaces, and long branched microvillous structures on the cell surface. Irregular dilatation of the perinuclear cisternae and mitochondrial swelling were also observed. This cell line was shown to be quite sensitive to antitumor agents, especially to certain alkylating agents, antimetabolites and antineoplastic antibiotics. It was concluded that this cell line may serve as a useful model of esophageal cancer for anticancer drug screening and other purposes. (10 Refs) (In CHI)

42. EXPERIMENTAL ANTITUMOR ACTIVITY OF A NEW NITROSOUREA DERIVATIVE, A CYSTEAMINE CHLOROETHYL NITROSOUREA: CNCC (MEETING ABSTRACT).

Mathe G, Maral R, Bourut C, Chenu E, Orbach-Arbouys S, Oiry J, Martinez J, Imbach JL
Hopital Paul-Brousse, Villejuif, France
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

A new nitrosourea derivative Di[(2-chloroethyl)-2N nitroso N carbamoyl]N,N-cystamine (CNCC) was synthesized in the hope that the cystamine link between two chloroethylnitrosourea parts would give favorable pharmacological properties to the molecule. The activity on L1210 leukemia was compared with that of chlorozotocin or 2[3-(2-chloroethyl(3-nitrosoureido]D-glucopyranose, RPCNU or (2-chloroethyl)-1-(ribopyranosyl triacetate-2'-3'-4')-3 nitrosourea, RFCNU or (2-chloroethyl)-1-(ribofuranosyl isopropylidene-2'3'-paranitrobenzoate-5')-3 nitrosourea and HECNU or 1-(2-hydroxyethyl)-3-(2-chloroethyl)-3 nitrosourea: the range of the doses giving the maximal activity is wider with CNCC. It was also studied in a large spectrum of other grafted murine tumors, namely in Lewis lung carcinoma (3LL), melanocarcinoma B16, glioma 26 and mammary carcinoma TM2: the activity of CNCC compares favorably with that of the other derivatives, principally in 3LL, glioma 26 and L1210 leukemia grafted intracerebrally. In the fields of immunology, it acts as the other nitrosoureas, but is slightly less immunodepressive than RFCNU or chloroxotocin. Using the Ames' test, it is as mutagenic as the other analogs. The cross-resistance with different nitrosoureas will be discussed. (no Refs)

43. IN THE SEARCH FOR NEW ANTICANCER DRUGS, II ANTITUMOR ACTIVITY, TOXICITY AND ELECTRON SPIN RESONANCE OF SPIN LABELED THIO-TEPA DERIVATIVES.

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Z Naturforsch [B]; 36(12):1612-1617 1981

The spin labeled analog of Thio-Tepa, 1-oxyl-2,2,6,6-tetramethyl-4-piperidyl-N,N;N',N'-bis (ethylene)-phosphorodiamidothioate (SL-O-TT), which contains a nitroxyl free radical linked by an oxygen bridge to phosphorus, has antitumor properties against P388 murine leukemia (T/C = 242) and a higher therapeutic ratio (5.15) than its parent compound, Thio-TEPA (2.75). The drug is less toxic to P388 cells in culture as judged by the 3H-thymidine uptake. On the basis of electron spin resonance spectroscopy using L1210 cells incubated with SL-O-TT, it is concluded that the drug is bound to cells in culture in such a way as to restrict the motion of the nitroxyl label. A second spin labeled analog, 1-oxyl-2,2,6,6-tetramethyl-4-amino-piperidyl-N,N;N',N' bis (ethylene)-phosphorodiamidothioate (SL-NH-TT), containing a nitroxyl label linked by a nitrogen bridge to phosphorus, first synthesized by Russian workers, was prepared by an improved procedure in 95% yield. In vivo results indicate that this analog has about the same therapeutic value (2.73) as Thio-TEPA (2.75), and that higher doses of this compound are required than those for both the O-bridged analog and Thio-TEPA to achieve maximum T/C values. (Author abstract) (20 Refs)

44. STUDIES ON TENUAZONIC ACID ANALOGS. V. SYNTHESES AND ANTITUMOR ACTIVITIES OF INDANE-1,3-DIONE DERIVATIVES.

Matsuo T, Takagi T, Saito K, Yuki H, Yamaguchi T

Res. Lab., Morishita Pharmaceutical Co. Ltd., 1658, Ohshinohara, Yasu-cho, Yasu-gun, Shiga, 520-23, Japan

Yakugaku Zasshi; 101(10):960-964 1981

Thirty-two derivatives of indane-1,3-dione were synthesized and screened both for cytostatic activity in vitro and for antitumor activity in vivo against sarcoma 180 cells. Of the 32 compounds, 2-(alpha-anilinobenzylidene)-indane-1,3-dione showed antitumor activity in vivo following ip and po administration despite lack of in vitro tumor growth inhibition. (8 Refs) (In JPN)

45. MAMMARY TUMOR INHIBITING EFFECT OF 3,3'-DIACETOXY-ALPHA,BETA-DIALKYLSTILBENES AND OF RELATED STILBENE OXIDES.

Schneider MR, Schonenberger H, Michel RT, Fortmeyer HP

Institut fur Pharmazie der Universitat Regensburg, Universitatsstrasse 31, D-8400 Regensburg, W. Germany

J Med Chem; 25(2):141-145 1982

The compounds 3,3'-Diacetoxy-alpha,beta-dialkylstilbenes (alkyl = CH3 to C4H9, 1-4), 3,3'-dihydroxy-alpha,beta-diethylstilbene (5), and their corresponding oxides were synthesized. Compounds 1-10 competitively antagonized in vitro the interaction of [3H]estradiol with its receptor. 3,3'-Diacetoxy-alpha,beta-diethylstilbene (2), 3,3'-diacetoxy-alpha,beta-diethylstilbene oxide (7), and their phenolic analogues (5 and 10) were most effective. Shortening or lengthening the alkyl side chains led to a decrease in receptor affinity. Among the stilbenes and epoxides, those with C2H5 and C3H7 groups (2,3,5 and 7,8,10) caused the strongest inhibition of the growth of a hormone-dependent postmenopausal human mammary carcinoma serially implanted in nude mice. The strong antitumor activity of 5 and 10 was confirmed by experiments on the 9,10-dimethyl-1,2-benzanthracene-induced, hormone-dependent mammary carcinoma of the Sprague-Dawley rat. (Author abstract) (10 Refs)

46. DEACYLCORTIVAZOL, A POTENT GLUCOCORTICOID WITH UNUSUAL STRUCTURE AND UNUSUAL ANTI-LEUKEMIC CELL ACTIVITY.

Thompson EB, Simons SS, Harmon JM

Lab. Biochemistry, Div. Cancer Biology and Diagnosis, NCI, Bethesda, MD, 20205

Adv Exp Med Biol; 138:315-324 1982

Induction of tyrosine aminotransferase (TAT) and lympholysis of T-derived leukemic lymphoblasts by deacylcortivazol (DAC) were investigated in HTC rat hepatoma cells and CEM-C7 human acute leukemic lymphoblasts. Two toxic effects on lymphoblasts were observed: the classic glucocorticoid effect with high potency and the ability of the compound to kill completely glucocorticoid-resistant clones irrespective of their residual receptor content. DAC was approx 400x more potent than cortisol in inducing TAT. DAC and similar compounds may have chemotherapeutic potential for certain blood dyscrasias. (22 Refs)

47. COMPARATIVE ANTIOESTROGEN ACTION IN EXPERIMENTAL BREAST CANCER.

Jordan VC

Dept. Human Oncology and Pharmacology, Wisconsin Clinical Cancer Center, Univ. Wisconsin, 600 Highland Ave., Madison, WI, 53792

Adv Exp Med Biol; 138:165-178 1982

A comparative assay system based upon the treatment of animals with early microfoci of carcinogen transformed breast cells by a 1 mo course of antiestrogen therapy was devised. Effectiveness of therapy in controlling the future development of tumors was studied using the assay. In the 7,12-dimethylbenz(a)anthracene-induced rat carcinoma mammary model, tamoxifen appears to be a more potent antitumor agent than the short acting monohydroxytamoxifen. (19 Refs)

48. SYNTHESIS AND ANTITUMOR ACTIVITY OF GLYCOPEPTIDES CONTAINING THE N-ACETYLGLUCOSAMINYL-(BETA 1-4)-N-ACETYLMURAMYL-DISACCHARIDE GROUP.

Rostovtseva LI, Andronova TM, Mal'kova VP, Sorokina IB, Ivanov VT

M. M. Shemiakin Inst. Bioorganic Chemistry, Moscow, USSR

Bioorg Khim; 7(12):1843-1858 1981

Syntheses of fragments and analogs of glycopeptides from the bacterial wall are described. Glucosaminylmuramyldipeptide (GMDP) was effective against Crocker sarcoma 180; max necrosis of the tumor was observed at a dose of GMDP of 50-100 mg/kg. The GMDP was less effective at 200 mg/kg. The GMDP was also effective against melanoma B-16, sarcoma 37, sarcoma 298, and Jensen sarcoma, but failed to inhibit the growth of leukemia L-1210 or of colonic adenocarcinoma. Analysis of the structure-activity relationships showed that shortening of the peptide chain of the GMDP was associated with a decrease in antitumor activity. Elongation of the carbohydrate chain was associated with less pronounced tumor necrosis but with more marked inhibition of tumor growth. (40 Refs) (In RUS)

49. PHASE I AND II STUDIES WITH 4,6-BENZYLIDINE-D-GLUCOSE (MEETING ABSTRACT).

Kochi M, Amemiya K

Ichijokai Hospital, Chiba, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

BG (4.6-benzylidene-D-glycose) is soluble in water and can be used iv or im. Toxicity of BG in both animals and human being is very slight. BG indicated remarkable antitumor activity against Walker 256 tumor in rats. BG also showed some antitumor activity against Ehrlich carcinoma and adenocarcinoma 755 in mice. These antitumor activities were similar to those of beta-cyclodextrin benzaldehyde inclusion compound (CDBA). In human cancer more than 375 mg of BG were injected iv bid. So far squamous cell carcinoma of tongue, liver tumor and brain tumor responded markedly. Squamous cell carcinoma treated with BG showed extremely differentiated pearls histologically which were observed in squamous cell carcinoma treated with CDBA. (no Refs)

50. BIOCHEMICAL AND PHARMACOLOGIC PROPERTIES OF A NEW FOLATE ANALOG, 10-DEAZA-AMINOPTERIN, IN MICE.

Sirotnak FM, DeGraw JI, Chello PL, Moccio DM, Dorick DM

Lab. Molecular Therapeutics, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

Cancer Treat Rep; 66(2):351-358 1982

Single-dose LD50 for 10-deaza-aminopterin in mice was 236 mg/kg compared to 28 and 386 mg/kg, respectively, for aminopterin and methotrexate. Multiple-dose LD10 for 10-deaza-aminopterin was 15 mg/kg (every 2 days x 5) compared to 0.4 and 18 mg/kg, respectively, for aminopterin and methotrexate. The rate of clearance of 10-deaza-aminopterin and methotrexate from mouse plasma was essentially the same following sc administration of 12-48 mg/kg. The clearance kinetics following oral administration of 48 mg/kg of each agent was also similar. However, following oral administration of 6 mg/kg, plasma levels were twofold higher for 10-deaza-aminopterin. Inhibition of tumor cell dihydrofolate reductase was essentially the same for 10-deaza-aminopterin, aminopterin, and methotrexate. The differences in lethal potency of 10-deaza-aminopterin and methotrexate correlated with the persistence of exchangeable levels of each agent in mouse small intestine. The differences in antitumor effects on L1210 leukemia an d Sarcoma 180 models shown for 10-deaza-aminopterin and methotrexate during earlier studies also correlated with the persistence of exchangeable levels of each agent in the tumor cell population after sc administration in vivo. The extent of persistence of each antifol in tumor or small intestine could be accounted for by differences in membrane transport, specifically the apparent influx Km, which is a measure of the affinity of the transport system in each cell type for the three analogs. These differences also correlated with the relative inhibitory potency of the three analogs against L1210 leukemia cells in culture. The greater antitumor efficacy against L1210 leukemia and Sarcoma 180 tumors in vivo observed earlier with 10-deaza-aminopterin compared to methotrexate and aminopterin appears to reflect a more favorable relative interaction of the new analog with the respective transport system in tumor compared with normal proliferative tissue in small intestine. (Author abstract) (24 Refs)

51. POTENTIAL ANTINEOPLASTIC AGENTS-III: SYNTHETIC AND PHARMACOLOGICAL STUDIES ON SOME N-ARYL-N'-2(4-P-ANISYL-5-ARYLAZOTHIAZOLYL) THIOCARBAMIDES.

Upadhyaya JS, Srivastava PK
Inst. Paper Technology, Univ. Roorkee, Saharanpur-247 001, India
J Indian Chem Soc; 58(8):789-791 1981

Antitumor activity of several thiocarbamides against L-1210 lymphoid leukemia cells was examined. Five of 30 compounds tested showed somewhat greater potency than the others; toxicity of the 30 compounds varied over a wide range. (16 Refs)

52. NITROGEN-CONTAINING ORGANOSILICON COMPOUNDS. COMMUNICATION IV. SYNTHESIS AND ANTINEOPLASTIC ACTIVITY OF AMIDES OF QUINOLINECARBOXYLIC ACIDS.

Lukevits E, Lapina TV, Sukhova NM, Zidermane AA, Dauvarte AZh, Voronova VA
Inst. Organic Synthesis, Riga, USSR
Khim Farm Zh; 15(11):53-56 1981

Antineoplastic activities of 13 newly synthesized amides of quinoline carboxylic acids were studied in random-bred mice bearing Ehrlich tumor, sarcoma 37, or sarcoma 180, in BDF1 mice bearing Lewis lung carcinoma, adenocarcinoma 755, leukemia L1210, or leukemia L5178Y, and in C57BL/6 mice bearing leukemia La. The amides (ip, days 1, 2, 3, 4, and 7 after tumor transplantation) were most effective against Ehrlich tumor (25-58% increase in life span), sarcoma 37 (38-42% increase in life span), and adenocarcinoma 755 (35-48% inhibition of tumor growth). (3 Refs) (In RUS)

53. THE EFFECT OF TETRANDRINE ON THE GROWTH OF ECA 109 CELL LINE IN VITRO.

Wang R, Pan Q
Cancer Inst., Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Zhonghua Zhongliu Zazhi; 3(2):86-88 1981

Tetrandrine an alkaloid isolated from Stephania tetrandra S Moore, which has been shown to have antimicrobial, antiinflammatory, analgesic, hypotensive and antitumor activities . Its effects on cell proliferation are described for long-term monolayer cultures of human esophageal cancer epithelial cell line (ECa 109) and the cloned line (Eca 109-C3). Tetrandrine caused complete detachment of ECa 109 cells from culture vessel after 48 hr of treatment at 75 ug/ml, and it caused most nucleoli of ECa 109-C3 cells to appear blurred at 10 ug/ml. Its effects on the mitotic index of both lines were essentially the same. At 7.5-10 ug/ml, tetrandrine inhibited mitotic index by 30-70%, with effects at 48 hr slightly stronger than those at 24 hr. At 1 ug/ml its effects on mitotic activities were only minimal. After exposure of ECa 109-C3 cells to 10 ug/ml tetrandrine for 5 days the growth was inhibited by 37% as compared to the control. Tetrandrine at 7.5-10 ug/ml also inhibited 3H-TdR incorporation in both cell lines by about 25%. Cell division was not affected in cells that had already synthesized DNA. (7 Refs) (In CHI)

54. CARCINOSTATIC EFFECT OF A CAFFEINE-8-ETHER-PLATINUM COMPLEX.

Kroger H, Klosa J
Robert Koch-Institut, D-1000 Berlin, W. Germany
Naturwissenschaften; 68(12):628 1981

Carcinostatic effect of di-[8-(3',3'-dimethylaminopropoxy)-caffeine]-hexachloro platinate (Cofplaton) is reported. Cofplaton effected complete or partial remissions of solid and ascitic Ehrlich tumors and sarcoma 180 in mice and Yoshida sarcoma in rats. Cofplaton was as effective as cis-platinum (CP), but did not have the toxicity of CP. (5 Refs) (In GER)

55. LIPOPHILIC 5'-(ALKYL PHOSPHATE) ESTERS OF 1-BETA-D-ARABINOFURANOSYLCYTOSINE AND ITS N4-ACYL AND 2,2'-ANHYDRO-3'-O-ACYL DERIVATIVES AS POTENTIAL PRODRUGS.

Rosowsky A, Kim SH, Ross J, Wick MM
Sidney Farber Cancer Inst., Boston, MA, 02115
J Med Chem; 25(2):171-178 1982

Lipophilic 5'-(alkyl phosphate) esters of 1-beta-D-arabinofuranosylcytosine (ara-C) and several N4-acyl and 3'-O-acyl-2,2'-anhydro derivatives of ara-C were synthesized as potential prodrugs of ara-C 5'-monophosphate (ara-CMP). Alkylphosphorylation of ara-C,N4-palmitoyl-ara-C, and N4-stearoyl-ara-C was achieved in a single continuous operation by allowing the nucleoside to react with POCl3 in trimethyl or triethyl phosphate and adding the appropriate anhydrous alcohol directly to the intermediate phosphorodichloridate without isolation. Similar reaction of cytidine yielded cytidine 5'-(alkyl phosphate) esters, which on treatment with myristoyl or palmitoyl chloride in the presence of boron trifluoride gave 3'-O-acyl-2,2'-anhydro-ara-C 5'-(alkyl phosphate) esters. Ara-C 5'-(n-butyl phosphate) (1b), N4-palmitoyl-ara-C 5'-(n-butyl phosphate) (1h), and 2,2'-anhydro-3'-O-palmitoyl-ara-C 5'-(n-butyl phosphate) (2h) were tested against L1210/ara-C leukemia in mice in the hope that this kinase-deficient tumor would respond to treatment with these 'prephosphorylated' derivatives, but no activity was observed. Of the simple 5'-(alkyl phosphate) esters tested in culture against L1210 leukemic cells, only ara-C 5'-(glyceryl phosphate) (1g) showed toxicity comparable to ara-CMP (ID50 = 0.35 and 0.65 uM, respectively), suggesting that beta-hydroxyalkyl phosphate esters may be worthwhile to examine further as prodrugs of ara-CMP. (Author abstract) (38 Refs)

56. ANTITUMOR ACTIVITY OF ASCORBATE AND COPPER/GLYCYLGLYCYLHISTIDINE COMPLEX AGAINST EHRLICH ASCITES CARCINOMA CELLS IN MICE (MEETING ABSTRACT).

Kimoto E, Morishige F

Department of Chemistry, Fukuoka University, Fukuoka, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Antitumor activity of ascorbate, in cooperation with cupric ion, has been reported by several workers. To apply this mechanism in vivo, we used the innocuous form of cupric ion complexed with glyclyglycylhistidine (GGH), a peptide molecule designed to mimic the specific Cu (II) transport site of albumin. Though a square planar Cu/GGH complex did not significantly oxidize the ascorbate at pH 7.4, it killed Ehrlich carcinoma cells in the presence of ascorbate in vitro and prolonged the life span of mice intraperitoneally inoculated by Ehrlich carcinoma cells. The target specificity against carcinoma cells might be attributable partially to the strong reducing power and the increased glycolysis (decrease in intracellular pH as measured by 31P nuclear magnetic resonance). (no Refs)

STUDIES OF ANTIMETASTATIC AGENTS

57. AN EXPERIMENTAL APPROACH TO CHEMOTHERAPY FOR OCCULT METASTASES: A QUANTITATIVE MODEL.

Speakman H, Dixon B

Univ. Dept. Radiotherapy, Cookridge Hosp., Leeds LS16 6QB, England

Eur J Cancer Clin Oncol; 17(12):1287-1293 1981

The population doubling time (PDT) of LMC1 tumor cells in axillary and inguinal lymph nodes of tumor-bearing rats was estimated during the occult development of secondary tumors. Values increased with time and 13 days after implantation of the primary the PDT and the mean cell cycle time were the same, suggesting all tumor cells were in cycle. This information was used to predict the optimum time for administration of cyclophosphamide (CP) and to design rational treatments combining surgery with chemotherapy. 150 mg/kg CP, given 13 +-1 days after implantation of the primary, reduced the incidence of metastases from 50% (in the surgery alone group) to zero. If the primary was left in situ reseeding was rapid and the incidence of metastases increased with time from drug administration. Within 13 days 50% of rats had metastases. However, a second dose of 150 mg/kg CP given at this time again reduced the incidence rate from 50% to zero. Lymph node metastases in rats given surgery alone reached 8-10 mm mean diameter (T8-10) 47.0 +-3.0 days after implantation of the primary. The equivalent T8-10 values for metastases reseeded from once- and twice-treated primary tumors should be about 60 (47 + 13) and 73 (47 + 26) days respectively. The observed values were 57.4 +-6.0 and 57.6 +-2.6 days. The reduced value for twice-treated animals suggest a greater number of cells present than expected, and this may be due to either an increase in 'seeding' efficiency or in the number of clonogenic cells shed from the primary tumor after the second dose of CP. (Author abstract) (17 Refs)

58. ANTIMETASTATIC EFFECTS AND TUMOR PROTEINASE INHIBITION BY SPLEEN INTRACELLULAR INHIBITORS OF NEUTRAL PROTEINASES.

Giraldi T, Sava G, Kopitar M, Brzin J, Suhar A, Turk V

Istituto di Farmacologia, Universita di Trieste, I-34100 Trieste, Italy

Eur J Cancer Clin Oncol; 17(12):1301-1306 1981

The mechanism of the antimetastatic effects of spleen intracellular inhibitors of neutral proteinases (SNPI's) has been examined in mice bearing subcutaneous Lewis lung carcinoma. SNPI-1 and SNPI-2 selectively depress the formation of spontaneous lung metastasis. A dose-dependent inhibition of the proteolytic activity of subcutaneous primary tumor homogenate at neutral pH was observed after ip administration of SNPI-1; its selective antimetastatic effects were evident only at the lower dosage used. This finding indicates that the administration of SNPI's, in spite of causing a dose-dependent depression of tumor proteinases, which presumably participate in the early phases of the process of metastasis formation, may also exert other actions, reducing their antimetastatic effects. (Author abstract) (46 Refs)

INTERFERON AND OTHER ANTIVIRALS

59. ALTERED PHARMACOLOGICAL PROPERTIES OF LIPOSOME-ASSOCIATED HUMAN INTERFERON-ALPHA.

Eppstein DA, Stewart WE

Inst. Bio-Organic Chemistry, Syntex Res., Palo Alto, CA, 94304

J Virol; 41(2):575-582 1982

Human interferon-alpha was associated in different ways with positively (stearylamine) and negatively (phosphatidylserine) charged phosphatidylcholine multilamellar vesicles, depending on the presence or absence of a cholesterol component. Inclusion of cholesterol resulted in interferon that was significantly ($p = 0.0001$) more deeply internalized within the liposomes, such that detergent disruption was necessary before most of the interferon activity was expressed. Interferon was stably associated with stearylamine-containing liposomes, both with and without a cholesterol component. However, inclusion of cholesterol in the phosphatidylserine-containing liposomes was necessary for stable association of the interferon for more than 2 days at 4 C or for more than 24 hr at 37 C. After intramuscular injection into mice, liposome-associated interferon in reverse-phase evaporation vesicles was retained at the local site of injection significantly longer than free interferon. Even 3 days after intramuscular injection, stearylamine-containing liposomes with or without cholesterol resulted in local interferon levels that were comparable to the peak levels obtained 2 to 4 hr after free interferon was injected. In contrast, free interferon was not detectable in the local muscles 24 hr after injection of 104.6 U. Liposomes containing phosphatidylserine and cholesterol resulted in intermediate levels of local interferon retention; without a cholesterol component, phosphatidylserine-containing liposomes resulted in no increased local interferon retention compared with the results when free interferon was injected. (Author abstract) (22 Refs)

60. ANALYSES OF THE EFFECT OF INTERFERON ON TUMOR CELL GROWTH UNDER IN VITRO AND IN VIVO CONDITIONS (MEETING ABSTRACT).

Uno K, Inaba K, Mori S, Oko T, Kishida T, Muramatsu S
Department of Zoology, Kyoto University, Kyoto, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Mouse brain and L interferons (IFN) inhibited the growth of fibrosarcoma (Meth A, BALB/c) under in vitro conditions. In vivo, however, neither solid nor ascites form of Meth A was hardly affected by IFN. This cannot be ascribed to a rapid catabolism of IFN in vivo, since the growth of tumor cells in diffusion chambers implanted ip was significantly inhibited by ip injection of IFN. Apparent resistance of in vivo tumor cells to IFN was analyzed in relation to the host immunological defense mechanism. (no Refs)

61. EFFECT OF N RUBRA-CWS ON VIRUS NON-PRODUCING RSV-INDUCED TUMORS WITHIN B10 CONGENIC AND RECOMBINANT MICE (MEETING ABSTRACT).

Haraguchi S, Kurakata S, Matsuo T, Awashima F, Kuzumaki N, Yoshida TO
Department of Microbiology, Hamamatsu University School of Medicine, Hamamatsu, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

We have previously reported that the development and growth of B10 tumors and B10A (5R) tumor were completely inhibited, but B10A tumors were not inhibited at all in the Rous sarcoma virus (RSV)-induced syngeneic mouse tumor systems using the id injection of tumor cells mixed with Nocardia-rubra cell wall skeleton (N-CWS). In this report we present the effect of intra-tumor injection of N-CWS using the above systems. The living cultured tumor cells (1x10(6)) were inoculated id. N-CWS (100 ug) was weekly injected into tumors after the tumor diameters became 4-5 mm. The growth of B10 tumor treated intratumorly with N-CWS was dramatically inhibited, and the tumor regressed completely in B10 mice previously immunized with Mitomycin C treated B10 tumor cells plus N-CWS. In B10A mice we could not observe the effect. (no Refs)

62. EFFECT OF HUMAN LEUKOCYTE INTERFERON ON YOLK SAC TUMOR TRANSPLANTED IN NUDE MICE (MEETING ABSTRACT).

Sawada M, Hayakawa K, Matsui Y, Nishiura H, Okudaira Y, Kishida T, Kurokawa K
Department of Gynecology, Osaka University, Osaka, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Human yolk sac tumor of the ovary transplanted in BALB/C nude mice designated as YST-2 was used in this experiment. YST-2 tumor cells preserve the characteristics of a human yolk sac tumor of the ovary, and were capable of producing alpha-fetoprotein (AFP). Four x 10 IU of human WBC interferon (HLIF) was administered ip to tumor-bearing nude mice everyday for eight days. Evaluation of response was made by examining tumor size, relative tumor size, serum AFP level of mice, tumor/control % (T/C) and histologic appearance. Optimal relative tumor size of treated tumor was 0.76 while that of the control tumor was 4.0. T/C% at the end of the experiment was 90.1. The level of AFP showed good correlation with the size of tumor. Histologic changes were recognized in treated tumor. HLIF was active in regressing of human yolk sac tumor. (no Refs)

63. SELECTIVE INHIBITION OF SV40-TRANSFORMED CELL GROWTH BY DIKETOPIPERAZINES.

Munekata M, Tamura G
Res. and Development Laboratories, Sapporo Breweries Ltd., Mita, Meguro-ku, Tokyo 153, Japan
Agric Biol Chem; 45(11):2613-2618 1981

Taxonomy of Streptomyces species strain ML1532, and isolation, characterization, and structures of the active substances produced by the strain were studied. Two diketopiperazines, cyclo(L-Val-L-Pro) and cyclo(L-Tyr-L-Pro) were isolated. Results showed that cytotoxicity of cyclo(L-Tyr-L-Pro) against SV40-transformed cells is slightly higher than that of cyclo(L-Val-L-Pro), and that the diketopiperazines may be metabolites of strain ML1532. (12 Refs)

64. REVERSAL BY HYPOTONIC MEDIUM OF THE ANTIVIRAL STATE INDUCED BY LYMPHOBLASTOID INTERFERON IN HUMAN HELA CELLS.

Munoz A, Carrasco L
(c/o Carrasco) Dept. Microbiology, Centro de Biologia Molecular, Universidad Autonoma, Canto Blanco, Madrid 34, Spain
Intervirology; 16(2):106-113 1981

The induction kinetics of the antiviral state in HeLa cells treated with human lymphoblastoid interferon (IFN) was studied. In cells treated with 4-200 U/ml IFN, the antiviral state was fully established in 7-9 hr. Inhibition of virus multiplication was more rapid if the concentration of IFN was increased to 1,000 U/ml. This antiviral state gradually disappeared during the 48 hr after IFN removal. Several compounds known to act on the cell membrane or on the cytoskeleton were tested for their influence on the establishment and reversal of the antiviral state. None of them were found to influence these two parameter s to a significant extent. In contrast, placing HeLa cells in medium lacking NaCl partially reversed the blockade to virus multiplication induced by IFN treatment. Cells treated with IFN and later placed in hypotonic medium synthesized virus proteins after encephalomyocarditis virus infection, although at a reduced level compared to cells that had not been treated with IFN. (Author abstract) (13 Refs)

65. ANTIVIRAL, ANTIMETABOLIC, AND CYTOTOXIC ACTIVITIES OF 5-SUBSTITUTED 2'-DEOXYCYTIDINES.

De Clercq E, Balzarini J, Descamps J, Huang GF, Torrence PF, Bergstrom DE, Jones AS, Serafinowski P, Verhelst G, Walker RT
Rega Inst. Medical Res., Katholieke Universiteit Leuven, B-3000 Leuven, Belgium
Mol Pharmacol; 21(1):217-223 1982

Several 5-substituted-2'-deoxycytidines (including 5-bromo-dCyd, 5-iodo-dCyd, 5-nitro-dCyd, 5-ethynyl-dCyd, 5-propyl-dCyd, (E)-5-(2-bromovinyl)-dCyd, (E)-5-(2-iodovinyl)-dCyd) were evaluated for their effects on herpes simplex virus (HSV: type 1 + type 2) and vaccinia virus cytopathogenicity and multiplication in primary rabbit kidney (PRK) cell cultures. The effects of 5-substituted 2'-deoxycytidines on incorporation of radiolabeled precursors into DNA of PRK or murine L1210 cells were studied and incorporation pathways hypothesized. L1210 tumor cell growth under the influence of the compounds was examined. The 5-X-deoxyuridine derivatives that are not selective as antiherpes agents became specific inhibitors of HSV replication when converted to dCyd counterparts, whereas 5-X-dUrd derivatives that are highly selective in antiherpes activity retained their specificity after amination to dCyd analogues. The compounds were relatively weak against tumor cell proliferation. (31 Refs)

OTHER RELATED STUDIES

66. TUMOR GROWTH INHIBITION BY INDOMETHACIN IN MICE (MEETING ABSTRACT).

Jenkin B, Sundharadas G
Center for Immunological Sciences, University of Wisconsin, Madison, WI
Tenth Annual Meeting Midwest Autumn Immunology Conference, Oct 18-20, 1981, Minneapolis, Minnesota University of Minnesota; 1981

The growth of a subcutaneously transplanted mouse tumor, Lewis Lung Carcinoma (LLC), was completely inhibited by administration of indomethacin, an inhibitor of prostaglandin synthesis, in the drinking water. No tumor growth was evident in indomethacin-treated mice, even after drug withdrawal. These results support the hypothesis that progressive tumor growth may be related, in part, to the immunosuppressive nature of prostaglandins released from tumor cells. (no Refs)

67. INTERACTIONS BETWEEN 5-FLUOROURACIL AND ALLOPURINOL, OROTIC ACID AND L-ASPARAGINASE IN NORMAL AND EL 4 ASCITES TUMOR BEARING MICE (MEETING ABSTRACT).

Pommier Y, Lokiec F, Marty M, Gisselbrecht C, Najean Y
Hopital Saint-Louis, 75010 Paris, France
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Increasing interest has developed in the modulation of 5-Fluorouracil (5-FU) effects by drugs interferring in its metabolism. Allopurinol (HPP) has been reported to increase the therapeutic index of 5-FU by reducing its toxicity. This effect seems to be mediated through an accumulation of orotidylate and orotic acid (OA) which in turn inhibit phosphorylation and activation of 5-FU. L-asparaginase (L-aspa) is a non specific proteolytic enzyme which has been reported to reduce the cytotoxic activity of methotrexate. In the present experiments, the modulation of the toxicity and antitumor activity of 5-FU by HPP, OA and L-aspa were studied. Toxicity was evaluated in normal C57BL/6 mice after single injections of 5-FU (290 mg/kg, ip). Antitumor activity was studied in C57BL/6 mice inoculated ip with 10(7) EL4 tumor cells and treated with 5-FU (20 mg/kg, ip, daily for 8 days). HPP (50 mg/kg) and L-aspa (500 IU/kg) were injected ip prior to 5-FU in all modulation experiments. HPP reduced both the toxicity and the antitumor activity of 5-FU. OA reduced 5-FU toxicity without reducing its antitumor activity. L-aspa slightly reduced the toxicity of 5-FU without modifying its antitumor activity. HPP, OA and L-aspa exhibited no antitumor activity when given alone. Differences between HPP and OA were quite unexpected since HPP has been reported to block 5-FU activation via an accumulation of OA. Combination chemotherapies of 5-FU and OA need further studies. (no Refs)

68. RESISTANCE OF PRENEOPLASTIC LIVER CELLS OF RATS TO MEMBRANE-ACTIVE AGENTS (MEETING ABSTRACT).

Sawada N, Furukawa K, Tsukada H
Department of Pathology, Cancer Research Institute, Sapporo Medical College, Sapporo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Normal and 2-acetylaminofluorene (2-AAF) induced preneoplastic (PN) liver cells of rats were isolated by collagenase perfusion methods. The cell suspension was mixed with phalloidin and incubated for 20 min at 37C. Percentage of the cells forming cytoplasmic blebs (phalloidin-sensitive cells) was smaller for PN cells than for normal cells. After 3 hr culture, the cells were incubated with phalloidin for 20 min, then they were fixed and stained for gamma-glutamyl transpeptidase (GGT). Bleb-formation of GGT-positive PN cells was lower in incidence than that of GGT-negative PN cells. Ca-ionophore, A23187, was added to the 24 hr culture and incubated for 1 hr. There was no difference in the cell viability between PN and normal cells, when determined by trypan blue exclusion test. D-galactosamine was added at the beginning of the culture in the presence of 3.6 mM Ca + +. Viability of the cells after 24 hr of the culture was higher for PN cells than for normal cells. It is suggested that resistance of PN cells to hepatotoxins includes alterations in the cell membranes. (no Refs)

69. CIRCADIAN TIME QUALIFIED CHEMOTHERAPY IN MELANOMA-BEARING MICE (MEETING ABSTRACT).

Takami H, Miyata J, Nakada M, Yamamoto O, Ogiwara H, Nishioka K, Abe O

Department of Surgery, Keio University, Tokyo, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

A marked circadian rhythm was observed in the level of S-adenosylmethionine decarboxylase SAMD. Methyl glyoxal-bis-guanylhydrazone (Methyl-GAG) inhibits SAMD in the polyamine metabolism. We determined whether the effect of methyl-GAG is influenced by circadian rhythm at the time the drug is administered. Forty-six DBA/2 mice were divided into 3 groups and injected with 1 x 10(5) melanoma cells iv at 8 AM, 4 PM, or 10 PM on day 0. From day 1, they received methyl-GAG (50 mg/kg) ip at each time point every day for 4 wk. The results suggests that circadian stage of drug administration may be crucial to maximizing antitumor effect in tumor-bearing mice. (no Refs)

70. PROPHYLACTIC ANTITUMOR ACTIVITY OF ASCOFURANONE (MEETING ABSTRACT).

Andoh K, Hosokawa T, Tamura G, Magae J, Nagai K

Department of Agricultural Chemistry, University of Tokyo, Tokyo, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Ascofuranone (AF) is a fungal sesquiterpenoid isolated and structurally elucidated by the authors. AF shows an interesting prophylactic activity against L-1210 and some allogenic ascites tumor in mice. A single ip treatment of BDF1 mice with AF (6-8 mg/mouse) 1 wk prior to L-1210 challenge (10(2) cells) resulted in protecting 20-50% of the mice from tumor death. The mechanism of this prophylaxis seems to be different from immunostimulators, since it is unnecessary to previously immunize the mice with the none-viable L-1210 cell. In addition, all the survivors were unable to reject the second challenge of L-1210. AF exerted a similar prophylactic activity against Ehrlich and S-180 ascites tumor (10(6) cells). In the allogenic tumor/host systems, the survived mice rejected the second transplants that had previously been rejected. (no Refs)

71. CHEMOTHERAPEUTIC SUSCEPTIBILITY OF CO-CULTURED NORMAL HUMAN CFU-C AND HUMAN ACUTE MYELOGENOUS LEUKEMIA CELLS (HL-60) IN VITRO (MEETING ABSTRACT).

Himori T, Ohnuma T, Wakui A
Tohoku University, Sendai, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

We determined the chemotherapeutic susceptibility of normal colony forming units in culture (CFU-C) and established human acute myelogenous leukemia (AML) cells (HL-60) in co-culture. Nucleated marrow cells and HL-60 cells were mixed in 0.33% agar containing McCoy's 5a medium, 10% fetal calf serum, 0.1 ml of human placenta-conditioned medium and various concentrations of vincristine (VCR), cytosine arabinoside (ara-C) and daunorubicin (DNR) to a total of 1.1 ml. In the absence of chemotherapeutic agents, the CFU-C colony formation was inhibited with the increasing number of HL-60 cells. CFU-C is equal to or less sensitive than the leukemic cells in separate culture, but in co-culture it becomes more susceptible to VCR and DNR. These data indicate AML cells exert inhibitory effects on marrow CFU-C. In such a state, normal hematopoietic cells becomes more susceptible to certain chemotherapeutic agents. (no Refs)

72. DOSE RELATED EFFECTIVENESS OF TEMPERATURE ON CELL KILLING BY PEPLEOMYCIN (MEETING ABSTRACT).

Uehara Y, Hori M, Umezawa H
Institute of Microbial Chemistry, Tokyo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Cytotoxicity of pepleomycin (PEP; a new member of bleomycins) against L5178Y mouse leukemic cells in vitro was studied. After 1.5 hr exposure of cells to PEP at OC or 37C, cell proliferation rate during the first 48 hr (3-4 doublings in control) (A) and colony forming ability in soft agar medium (B) were compared. Greater inhibition of (A) was observed with cells treated at OC. However, high concentrations (50-100 ug/ml) of PEP acting on cells at 37C gave 10-100 x greater inhibition of (B) than the inhibition caused by the same range of PEP doses at OC. In contrast, low concentrations of PEP (5-10 ug/ml) gave no difference in the cell killing (B, 30-40% of control) between the treatments at the two temperatures. These results suggest that: (1) cells treated with any concentrations of PEP can divide several times before the entire progeny perishes from the lethal damage, and (2) the cell killing effect of PEP is consisted of two phases; one is dependent on temperature and caused by high concentrations of PEP and the other independent of temperature and by low concentrations of PEP. (no Refs)

73. STUDY ON SYNCHRONIZATION THERAPY FOR NEUROBLASTOMA (MEETING ABSTRACT).

Sasaki F, Naito H, Une Y, Adachi T, Hata Y, Uchino J, Kasai Y
1st Department of Surgery, Hokkaido University School of Medicine, Sapporo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The synchronization therapy for neuroblastoma was undertaken in in vitro and in vivo experiments. Uncloned C-1300 cell line treated by 10(-4) ug/ml of Vincristine (VCR) showed G2+M phase accumulation. The treatment of CPM (cyclophosphamide), (1x10(-2) ug/ml) 24 hr after VCR had a more cytocidal effect than the treatment of CPM+VCR (simultaneous) or VCR following CPM. The most inhibition effect on the growth of the tumor transplanted into the back of mouse was recognized in the group with CPM treatment 12 hr after VCR administration. (no Refs)

74. EVALUATION OF ANTICANCER AGENTS BY THE CYTOFLUIDITY AND UPTAKE-VELOCITY AS REVEALED BY FLUORESCENCE USING FLUORESCEIN DIACETATE (MEETING ABSTRACT).

Maeda H, Tsuda H, Takeshita J
Department of Microbiology, Kumamoto University School of Medicine, Kumamoto, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Fluorescein diacetate (FDA) is known to be taken up into viable cells but not into dead cells. FDA after incorporation into cells becomes fluorescent fluorescein which is utilized as a probe. It reveals two remarkable changes in cells when they are treated with antitumor drugs: One is suppression of FDA-uptake and the other is alteration of fluorescence polarization value (intracellular fluidity). We will present the results obtained with various antitumor drugs. Their effects are either time or concentration dependent. The result can be obtained very rapidly and sensitively and operation is simple. (no Refs)

75. EFFECT OF CHEMOTHERAPY AND RADIOTHERAPY ON GROWTH OF HUMAN RESPIRATORY AND EXCRETORY SYSTEM TUMORS TRANSPLANTED INTO ATHYMIC MICE.

Revazova ES
Cancer Res. Center, Moscow, USSR
Biull Eksp Biol Med; 91(11):593-596 1981

Efficacy of various antineoplastic agents and radiotherapy was studied in human lung cancer (LC), laryngeal cancer (LaC), kidney cancer (KC), and Wilms' tumor (WT) transplanted into athymic BALB/c mice. Animals bearing LC, LaC, KC, and WT received single or multiple ip injections of antineoplastic agents. Mice bearing LaC were subjected to whole-body irradiation (500 rads). LC and LaC were resistant to all antineoplastic agents tested. WT was sensitive to cyclophosphamide and dactinomycin. Radiotherapy resulted in a temporary inhibition of LaC growth. Resistance of KC to chemotherapy was associated with the presence in tumor tissue of multiple cavities filled with blood. (6 Refs) (In RUS)

76. A COMPARATIVE ASSESSMENT OF THE IN VITRO EFFECTS OF DRUGS ON CELLS BY MEANS OF COLONY ASSAYS OR FLOW MICROFLUORIMETRY.

Hill BT, Whelan RD, Rupniak T, Dennis LY, Rosholt HT
Lab. Cellular Chemotherapy, Imperial Cancer Res. Fund Lab., Lincoln's Inn Fields, London WC2A 3PX, England
Cancer Chemother Pharmacol; 7(1):21-26 1981

The use of flow microfluorimetric (FMC) analysis for drug sensitivity testing is reported. This procedure provides results within a few hr and allows a study of the kinetic effects of drugs on cells. In 24 hr drug exposures logarithmically growing murine neuroblastoma cells were treated with a range of concentrations of various antitumor drugs and their colony-forming ability was assessed. Depending on the drug used, survival curves had plateaus at as high a level as 50%, eg, with methotrexate (MTX), or at as low a level as 20%, eg with VM-26. Cell kill was consistently less after 1 hr exposures, even at increased drug concentrations. FMC analysis of 24 hr treated cells at lower drug concentrations (80% survival) showed noticeable arrest accumulation (1) at the G1/S boundary for 2,4-diamino-5-(3',4'-dichlorophenyl)-6-methyl pyrimidine (DDMP), 5-fluorouracil, MTX, and dramatically, hydroxyurea; (2) at the G2/M phases with melphalan, peptichemio, adriamycin, dibromodulcitol, bleomycin, razoxane, vincristine, and vindesine, and only slightly with cis-platinum; and (3) additionally in the S phase with dibromodulcitol, peptichemio, and melphalan. Higher drug concentrations (40% survival) of DDMP, 5-fluorouracil, MTX, or hydroxyurea resulted in a loss of G2/M populations. Melphalan, peptichemio, and cis-platinum all resulted in a pronounced accumulation of cells in the G2 and/or M phases where a block and/or cell kill has probably occurred. Substantial G1 populations, however, remained. Arrest was almost totally in the G2/M phases with a loss of both G1 and S phase cells after treatment with vincristine, vindesine, VM-26, VP-16-213, and razoxane. Treatment with adriamycin, bleomycin, and dibromodulcitol at these high dose levels resulted in a broad accumulation of most cells shifted away from G1 into S and G2/M phases. (22 Refs)

77. THE INFLUENCE OF ZINC STATUS ON THE ANTI-LEWIS LUNG TUMOUR ACTIVITY OF CISPLATIN AND GALLIUM.

Capel ID, Dorrell HM, Pinnock MH, Jenner M, Williams DC
Res. Dept., Marie Curie Memorial Foundation, The Chart, Surrey, RH8 OTX, England
Anticancer Res; 1(5):269-273 1981

Effects of treatment of Lewis lung tumors in male C57/Bl mice with cisplatin and gallium nitrate on tissue Zn levels were investigated. Antitumor activity of cisplatin in Zn-deficient and supplemented (av intake of 628 ug equivalents Zn/mouse/day) animals was also studied. Mice treated with cisplatin received an ip injection of 10 mg/kg on alternate days beginning either 5, 7, or 9 days after tumor inoculation. Gallium nitrate (11.6, 23.1, or 34.7 mg/kg) was administered ip 5 days after tumor inoculation. Animals given cisplatin for 5 alternative days after tumor inoculation had significantly smaller primary tumors and fewer pulmonary metastases than untreated mice. Gallium nitrate significantly inhibited both tumor growth and metastases only at 34.7 mg/kg, and the number of pulmonary tumor foci was significantly reduced by 23.1 mg/kg. At the efficacious dose levels of cisplatin and gallium nitrate, the Zn levels in the livers and tumors of treated animals were significantly lower than in tissues of untreated mice. Tumors of mi ce fed Zn-deficient diets were significantly smaller and the number of pulmonary metastases fewer than those of animals fed Zn-restricted or Zn-supplemented diets. Of the Zn-deficient mice, those treated with cisplatin had smaller primary tumors and fewer secondary lung foci than untreated mice. Prior administration of penicillamine enhanced the anti-Lewis lung tumor activity of cisplatin. Few animals receiving penicillamine prior to cisplatin therapy survived 14 days after tumor inoculation. These findings indicate that Zn deficiency limits tumor growth and that Zn supplementation might alter the therapeutic index of metal-containing antitumor agents. (25 Refs)

78. THE EFFECT OF HEROIN AND NALOXONE ON THE GROWTH OF NEUROBLASTOMA TUMORS IN MICE.

Zagon IS
Milton S. Hershey Medical Center, Hershey, PA, 17033
Natl Inst Drug Abuse Res Monogr Ser; 34:394-398 1981

Daily injections of heroin (H) alone (diacetylmorphine 6 mg/kg sc) and naloxone (10 mg/kg sc) + heroin (N + H) were given to male syngeneic A/Jax mice (6-8 wk old). Tumor cells (C1300 murine neuroblastoma) were sc injected (10(6) in 0.05 ml growth medium) after 2 wk of daily drug injections. Within 3 wk all control (C) mice and all mice receiving N + H had developed measurable tumors, but 2/10 of the H-only group did not develop tumors within 62 days after the first neuroblastoma inoculation. Mean survival time in mice in the H group was extended 35% compared to controls. The first death of a tumor-bearing, H-treated mouse occurred later than in C or N + H mice, and some of the H mice lived up to 3 wk after all control mice had died. The mean time of initial appearance of a measurable tumor was delayed by 45% in mice of the H-only group and by 23% in the N + H-group, but in N + H-mice the median day for initial tumor appearance, tumor growth between days 10 and 31, and tumor size at death were comparable to C mice. (12 Refs)

79. VITAMIN B6 AND CANCER (REVIEW).

Tryfiates GP, Morris HP, Sonidis GP
Dept. Biochemistry, West Virginia Univ. Sch. Medicine, Morgantown, WV, 26506
Anticancer Res; 1(5):263-267 1981

Effects of vitamin B6 (comprised of pyridoxine, pyridoxal, pyridoxamine, and their phosphorylated derivatives) on tumor growth are reviewed, particularly with respect to transplantable minimum deviation Morris hepatomas. When dietary pyridoxine was restricted, tumor growth was inhibited and enzyme activity was altered, especially in the presence of growing hepatomas. Supplementation of the diet with vitamin B6 stimulates tumor growth, shortens survival time of mice, and prevents an increase in the survival time of the tumor-bearing animals which were treated with 5-fluorouracil. Pyridoxine restriction appears to affect both transhydroxymethylase and synthetase by different mechanisms which synergistical ly augment tumor growth inhibition. When the vitamin complexing agent L-penicillamine (L-PEN) was injected into Buffalo rats bearing No 777 Morris hepatomas, vitamin B6 was inactivated in situ, and the animals became energetic and were able to care for themselves within 4 days. L-PEN forms a stable complex with pyridoxal 5'-phosphate in vivo and/or in vitro resulting in decreased aminotransferase activity levels. Even at advanced tumor stages, inactivation of vitamin B6 in situ can be highly beneficial for the host. (34 Refs)

80. TRANSPLANTATION RESISTANCE OF DRUG-TREATED ALLOGENEIC MICE AGAINST MURINE LYMPHOMAS--II. STUDIES WITH VARIOUS TUMOR-HOST COMBINATIONS.

Bonmassar A, Rivosecchi-Merletti P, Barzi A, Goldin A, Bonmassar E
Inst. Pharmacology, Univ. Perugia, Via del Giochetto, Perugia 06100, Italy
Int J Immunopharmacol; 3(4):391-399 1981

Strain distribution of localized lymphoma graft resistance was investigated in mice treated with cyclophosphamide (Cy) and 5(3,3'-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC). Lymphomas employed were two H-2d (L1210 and LSTRA), one H-2b (L5MF-22) and one H-2a (LAF-17). 125I-labeled-5-iodo-2'-deoxyuridine uptake was measured in the liver and spleen of leukemic mice pretreated with DTIC (100 mg/kg, ip 1 and 2 days prior to challenge) and Cy (250 mg/kg, ip on day 0, 5 hr before tumor transplantation). Tumor cell proliferation was markedly inhibited in the spleen and was either unaffected or weakly inhibited in the liver of D end Hh-1-incompatible euthymic or nude mice that were Hh-system responders. Spleen and liver of Hh-1-compatible B10.A(2R) mice were not resistant to L5MF-22 lymphoma. SJL recipients genetically non-responder for the Hh system had no resistance to LSTRA cells. Splenic resistance against L1210 leukemia was detectable in Hh-compatible B10.A or B10.A(5R) mice. Splenic and liver resistance was found in Hh-incompatible but genetically Hh non-responder SJL or C3H mice against L5MF-22 or LSTRA lymphomas, respectively. Results indicated that the genetic patterns of resistance in the spleen and liver of drug-treated hosts were similar to those previously found in lethally-irradiated mice. (45 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

ANTITUMOR AGENT EFFICACY IN VIVO

1. INHIBITION BY 17BETA-ESTRADIOL OF THE GROWTH OF THE RAT PITUITARY TRANSPLANTABLE TUMOR MTF4.

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Cancer Res; 42(4):1492-1497 1982

The effects of pharmacological doses of estradiol on the growth of the rat pitui tary transplantable tumor MtF4 have been characterized. After sc injection into control rats of a cell suspension prepared from the tumor, in 12 experiments, the av range of days when a new tumor became palpable was between 14.7 -2.3 (SD) and 24.5 -3.3. rats. Daily im injections of 10 ug 17beta-estradiol benzoate or 17beta-estradiol implanted in Silastic tubing partially inhibited the tumor growth as judged by the wt and the time of appearance of the tumor. The same treatments increased the pituitary wt. Both effects were dose dependent above 3 ug 17beta-estradiol benzoate per day and displayed some specificity. 17alpha-Estradiol did not modify the pituitary or the tumor growth significantly; 17beta-hydroxy-3-keto-5alpha-androstane also did not modify the tumor growth. The inhibitory effect of 17beta-estradiol on tumor growth has also been observed in hypophysectomized rats. The tumor cytosol contained 30 to 220 fmol of specific estrogen-binding sites per mg protein which were characterized by: a high affinity (Kd, 0.25 to 0.65 x 10-9M); a sedimentation constant of 6 to 8S; and their hormone specificity. Thus, 17alpha-estradiol, which was inactive in vivo, had an affinity only fourfold lower than 17beta-estradiol. We conclude that pharmacological doses of 17beta-estradiol inhibit in a dose-dependent manner and with some specificity the growth of the MtF4 transplantable pituitary tumor while increasing the growth of pituitary. We suggest this inhibition requires estrogen receptors and is not mediated via the pituitary, but we cannot specify whether this inhibition was direct or not. (31 Refs)

2. INHIBITION OF THE R3327MAT-LU PROSTATIC TUMOR BY DIETHYLSTILBESTROL AND 1,2-BIS(3,5-DIOXOPIPERAZIN-1-YL)PROPANE.

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Cancer Res; 42(4):1390-1394 1982

We have previously described the inhibitory effects of diethylstilbestrol on the growth of the androgen-independent, anaplastic Copenhagen rat prostatic tumor, R3327AT, which has a low metastatic potential. We have now selected a variant of the R3327AT tumor that metastasizes exclusively to the lungs, and we have designated it the R3327MAT-Lu. In a dose-response protocol, diethylstilbestrol was inhibitory to the primary R3327MAT-Lu tumor, thereby also inhibiting the formation of lung metastases. Inhibition was also observed in this model tumor by the chemotherapeutic agent 1,2-bis(3,5-dioxopiperazin-1-yl)propane. (Author abstract) (23 Refs)

3. THE EFFECT OF HARRINGTONINE AND AND ITS ALLIED ALKALOIDS ON THE INCORPORATION OF LABELED AMINO ACIDS INTO PROTEINS OF CELLS OF TRANSPLANTABLE LEUKEMIAS L-615 AND P-388.

Xu Y, Du C, Zhang F, Ji X

Inst. Materia Medica, Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Yaoxue Xuebao; 16(9):661-666 1981

Effects of four different harringtonines (herringtonine, homoharringtone, isoharringtonin, and deoxyharringtonine) on protein biosynthesis in experimental leukemias (L-615 and P388) are described. Tests for the effects consisted of the incorporation of tritium-labeled DL-leucine and L-asparagine and of carbon-14-labeled DL-phenylalanine into proteins of mouse leukemia P388 ascitic cells and L-615 splenic tissue. When 1/5 of the LD50 of any one of the alkaloids was injected ip or iv into mice bearing the leukemias, marked inhibition of protein synthesis was observed. The effects were rapid, with max inhibition observed 30 min to 4 hr after administration of the drug; recovery occurred after 24 hr. The alkaloids had similar time-effect curves. The significance of these results in relation to chemotherapy of leukemia is discussed. (17 Refs) (In CHI)

4. 4'-O-TETRAHYDROPYRANYLADRIAMYCIN AS A POTENTIAL NEW ANTITUMOR AGENT.

Tsuruo T, Iida H, Tsukagoshi S, Sakurai Y

Cancer Chemotherapy Center, Japanese Foundation Cancer Res., Toshima-ku, Tokyo 170, Japan

Cancer Res; 42(4):1462-1467 1982

Chemotherapy with 4'-O-tetrahydropyranyladriamycin (THP-ADM), a new derivative of Adriamycin, was equally or more effective against several experimental mouse tumors than it was with Adriamycin (ADM). When mice with P388 leukemia were given ip injections of THP-ADM or ADM daily for 9 consecutive days, the max increases in life span (ILSs) of the mice were 190 and 175%, respectively. Eight of 24 mice treated with THP-ADM was free of tumor, while 1 of 24 mice treated with ADM was free of tumor. A single ip injection of either drug was also effective; max ILS was 170% for mice treated with THP-ADM and 240% for those treated with ADM. Nine of 12 mice were found to be free of tumor. THP-ADM was equally or slightly more effective against P388 leukemia than was ADM when either drug was given iv. The max ILS was 106% with THP-ADM and 77% with ADM when the drug was given for 9 consecutive days. Single iv injections of THP-ADM or ADM were almost equally (ILS, 100%) effective. Chemotherapy with THP-ADM was also very effective against L1210 leukemia. THP-ADM administered ip 5x, every other day starting from Day 1, was more effective than ADM was against Lewis lung carcinoma, B16 melanoma, and colon adenocarcinoma 38 inoculated sc. In the study with Lewis lung carcinoma, metastasis to the lungs was well suppressed by THP-ADM. ADM was more effective than was THP-ADM against colon adenocarcinoma 26. Because THP-ADM was more cytotoxic than or almost equally as cytotoxic as ADM against the established cell lines from the above mouse tumors, we suggest that THP-ADM is more efficiently transported into cultured cells. (Author abstract) (12 Refs)

5. EFFECT OF ORAL ADMINISTRATION OF PROTEASE INHIBITOR [N,N-DIMETHYLCARBAMOYLMETHYL 4-(4-GUANIDINOBENZOYLOXY)-PHENYLACETATE] METHANESULFATE ON THE GROWTH OF 3-METHYLCHOLANTHRENE-INDUCED CARCINOMA IN MICE.

Ohkoshi M, Fujii S
Dept. Oral Surgery, Nagoya Univ. Sch. Medicine, 65, Tsurumai-cho, Show-ku, Nagoya 466, Japan
Gan; 73(1):108-110 1982

Oral administration of a synthetic protease inhibitor, [N,N-dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy)-phenylacetate] methanesulfate, was used to challenge 3-methylcholanthrene-induced carcinoma. This drug was administered 3x daily via a stomach tube at doses of 12.5, 25 and 50 mg/kg in 33 mice harboring solid tumors. Oral administration of more than 50.0 mg/kg of this protease inhibitor significantly inhibited tumor growth and prolonged the survival time of cancer-harboring animals (p less than 0.05). These results indicate that oral administration of an inhibitor of kinin-forming protease has an antitumor effect on malignant tumors. (Author abstract) (7 Refs)

6. STUDIES ON FUNGAL POLYSACCHARIDES. XXVII. STRUCTURAL EXAMINATION OF A WATER-SOLUBLE, ANTITUMOR POLYSACCHARIDE OF GANODERMA LUCIDUM.

Miyazaki T, Nishijima M
Tokyo Coll. Pharmacy, 1432-1 Horinouchi, Hachioji-shi, Tokyo 192-03, Japan
Chem Pharm Bull (Tokyo); 29(12):3611-3616 1981

A water-soluble polysaccharide (GL-1) extracted from the fruit bodies of Ganoderma lucidum, the source of the crude drug 'Reishi' which has been used against several disorders, is shown to consist of glucose, xylose, and arabinose in the molar ratio 18.8:1.5:1.0. Chromatographic, chemical, sedimentation, and nuclear magnetic resonance results led to the conclusion that GL-1 is an arabinoxyloglucan with highly branched structure possessing (1-4)-alpha- and -beta-, (1-6)-beta-, (1-3)-beta, (1-3), (1-6)-, and (1-4, 1-6)-linked D-glucopyranosyl residues. Arabinose may be present as part of the nonreducing terminal residues, whereas xylose may occur only as part of the side chains. Antitumor activity was assessed against 7-day-old Sarcoma 180 ascites transplanted sc into 5-wk-old female ICR mice. GL-1, plus GL-2 and GL-3, two fractions obtained by acid hydrolysis and alpha-amylase treatment, respectively, were injected ip daily for 10 days, starting 24 hr after tumor inoculation at doses of 5-20 mg/kg (daily). Concentration-dependent inhibition from 42-98.5% based on tumor weight, and complete regression ranging from 1/9-6/9 were observed. (19 Refs)

7. ANTILEUKEMIC EFFECTS OF 5-(2-DIMETHYLAMINOETHOXY)-7-OXO-7H-BENZO(C) FLUORENE, SUBSTANCE VUFB 13 468, ON L1210 AND LA LEUKEMIA.

Pujman V, Cernochova S
Res. Inst. Pharmacy and Biochemistry, 130 60 Prague 3, Czechoslovakia
Neoplasma; 28(6):715-720 1981

The antineoplastic effect of 5-(2-dimethyl-aminoethoxy)-7-oxo-7H-benzo(c) fluorene, substance VUFB 13 468, was studied in leukemia L1210 and leukemia La. It was found that the test substance, in the form of base and in the form of hydrochloride, influenced favorably the survival of leukemic mice, in which the life span increased in dependence on the dose and the scheme of its application. (Author abstract) (3 Refs)

ANTITUMOR AGENT EFFICACY IN VITRO

8. A COMPARISON OF ADRIAMYCIN AND MAMSA IN VITRO: CELL LETHALITY AND SCE STUDIES.

West C, Stratford IJ, Barrass N, Smith E

Radiobiology Unit, Physics Dept., Inst. Cancer Res., Clifton Ave., Sutton, Surrey SM2 5PX, England

Br J Cancer; 44(6):798-809 1981

We have compared the actions of Adriamycin (ADM) and mAMSA in Chinese hamster V79 cells in vitro, using cell survival and sister-chromatid exchange as end-points. Equimolar concentrations of ADM and mAMSA show similar toxicities to exponentially growing cells, and both drugs are less effective in killing chronically hypoxic and plateau-phase cells. Cytotoxicity to thermotolerant cells (41 C for 16 hr previously) shows little difference from that for exponential cells. Pretreating cells with misonidazole under hypoxic conditions reduces the toxicity of both ADM and mAMSA. In addition, an ADM-resistant Chinese hamster cell line, 77A-177, was cross-resistant to mAMSA. Finally, low equimolar sub-toxic doses of both drugs were found to cause similar increases in the levels of sister-chromatid exchanges in V79 cells. These results reveal no major difference in activity between ADM and mAMSA in vitro. (Author abstract) (35 Refs)

9. THE EFFECTS OF INHIBITORS OF DNA BIOSYNTHESIS ON THE CYTOTOXICITY OF 6-THIOGUANINE.

Lee SH, Sartorelli AC

Comprehensive Cancer Center, Yale Univ. Sch. Medicine, New Haven, CT, 06510

Cancer Biochem Biophys; 5(3):189-194 1981

The effects of hydroxyurea, 1-beta-D-arabinofuranosylcytosine, and 5-fluorodeoxyuridine on the antiproliferative activity of 6-thioguanine (6-TG) in exponentially growing L1210 leukemia cell cultures were measured by changes in (methyl-3H)thymidine, (U-3H)uridine, and (8-14C)adenine incorporation. None of the inhibitors of DNA biosynthesis caused additive toxicity when used with 6-TG but instead significantly decreased the delayed cytotoxicity of 6-TG, suggesting that cell injury caused by the agent is mediated at least in part through DNA synthetic processes. Cells exposed to 10 uM 6-TG for 30 min in G1/S or S phases of the cell cycle were considerably more susceptible to the cytotoxic action of 6-TG than those treated in G2 phase. However, some cytotoxicity was also evident after exposure in G2 phase, suggesting that multiple biochemical lesions account for the effects. Alkaline sucrose gradient sedimentation of L1210 cells exposed to 6-TG revealed that the purine analogue causes structural breaks in DNA. (35 Refs)

10. EFFECTS OF CYTOSINE ARABINOSIDE AND DAUNORUBICIN ON SURVIVAL AND CELL CYCLE PROG RESSION OF CHINESE HAMSTER OVARY CELLS.

Fried J, Perez AG, Doblin J, Clarkson BD

Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

Cell Tissue Kinet; 15(1):11-23 1982

Kinetic and cytotoxic effects of cytosine arabinoside (Ara-C) and daunorubicin (DNR) on exponentially growing Chinese hamster ovary (CHO) cells were measured by flow cytometry and by a colony-forming assay, respectively. With Ara-C alone, increasing drug concentrations between 10(-7) M and 10(-4) M, for up to 27 hr, were associated with increased inhibition of cell progression through the S phase. Even at the very toxic concentration of 10(-4) M, however, cells were able to enter and progress slowly through S. DNR, which appears to enter these cells relatively slowly, was highly toxic even at 2 x 10(-7) M. It decreased the rate of progression through S phase and caused cells to accumulate in G2, except at the highest concentration (2 x 10(-5) M), at which progression was inhibited throughout the cycle. Simultaneous exposure of the cells to Ara-C and DNR yielded cell cycle distributions similar to those of the former drug alone. When cells were exposed to a non-lethal dose of Ara-C and to a dose of DNR which was lethal to a fraction of the cell population (or conversely), either simultaneously or separated by a drug-free interval, small, but in some cases significant, drug interactions were observed. These effects were not caused by drug-induced redistribution of cells within the cell cycle, but may have been related to the effects of the non-lethal drug on DNA synthesis rate. (Author abstract) (25 Refs)

11. QUANTITATIVE DOSE-RESPONSE RELATIONS FOR THE CYTOTOXIC ACTIVITY OF CHLOROETHYLNITROSOUREAS IN CELL CULTURE.

Weinkam RJ, Deen DF

Dept. Medicinal Chemistry, Purdue Univ., West Lafayette, IN, 47907

Cancer Res; 42(3):1008-1014 1982

A dose-response relation for the cytotoxic activity of chloroethylnitrosourea cancer chemotherapeutic agents in cell culture has been developed. Data for the activity of 1,3-bis(2-chloroethyl)-1-nitrosurea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1 nitrosourea, and 1-(2-chloroethyl)-3-(piperidine-3,6-dion-3-yl)-1 nitrosourea against 9L rat brain tumor cells are presented. Cytotoxicity resulting from treatment schedules at different initial drug concentrations, exposure periods, and preincubation periods are correlated using a proposed dose function. Equations are presented that incorporate drug concentration, duration of exposure of cells, and the rate constant for conversion of the drug from an active intermediate into a single dose function. When compared in this way, all cell treatment schedules used were found to be equally effective in killing cells in culture. The cytotoxic activity of the four different chloroethylnitrosourea analogs were also found to be the same. These data demonstrate the application of quantitative dose-response relations to the activity of chloroethylnitrosoureas in cell culture and provide new insight into the mechanism of action and structure-activity relationships of these compounds. (Author abstract) (52 Refs)

12. THE EFFECT OF LH1, AN AMINOACYL-STEROID, ON CULTURED HEPATOMA CELLS.

Giesen EM, Beck JP, Beck G, Nguyen-Dang T

Institut de Biologie Moleculaire et Cellulaire du CNRS, 15-21, rue Descartes, 67084 Strasbourg, France

Cancer Biochem Biophys; 5(4):233-238 1981

LH1, synthesized from 3alpha-amino-5-alpha-pregnane-20-one and N-protected glycine, was used in experiments on HTC cells from clone 7288C of Morris hepatoma in the rat. LH1 penetrated rapidly into cells, at a rate comparable to that of dexamethasone. LH1 exerted a powerful cytoxic effect on HTC cells: half maximal growth inhibition after 1 day was obtained at 15 ug/ml, and after 3 days at 6 ug/ml; 53 ug/ml killed all cells after 1 day, and 30 ug/ml killed all cells after 2-3 days. Logarithmically growing cells were more sensitive than quiescent cells. DNA and RNA synthesis, measured by (3H)thymidine and (3H)uridine incorporation, respectively, were inhibited reversibly below a threshold concentration of 30 ug LH1/ml of cell suspension. LH1 has even more severe inhibitory effects on protein synthesis, and the threshold concentration is lower, suggesting that DNA and RNA synthesis effects may be secondary (low LH1 concentration) or due to a different mechanism of action (high LH1 concentration). (14 Refs)

13. COLLATERAL SENSITIVITY OF 6-MERCAPTOPURINE-RESISTANT SUBLINES OF P388 AND L1210 LEUKEMIA TO THE NEW PURINE ANTAGONISTS, 5-CARBAMOYL-1H-IMIDAZOLE-4-YL PIPERONYLATE AND 4-CARBAMOYLIMIDAZOLIUM 5-OLATE.

Inaba M, Fukui M, Yoshida N, Tsukagoshi S, Sakurai Y

Cancer Chemotherapy Center, Japanese Foundation Cancer Res., Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan

Cancer Res; 42(3):1103-1106 1982

Two new purine antagonists, 5-carbamoyl-1H-imidazol-4-yl piperonylate (SL-1250) and 4-carbamoylimidazolium 5-olate (SM-108), were investigated for their antitumor activities against 6-mercaptopurine (6-MP)-resistant sublines of P388 and L1210 leukemia. It was found that both resistant sublines exhibited collateral sensitivity instead of cross-resistance to these new antipurine drugs. Since more potent cytotoxic activities of these drugs against 6-MP-resistant cells were observed even in in vitro cell culture systems, this collateral sensitivity was proved on a cellular basis. Biochemical studies revealed that 6-MP-resistant sublines of both P388 and L1210 leukemia are deficient in hypoxanthine guanine phosphoribosyltransferase activity. In these cells, not only the activation of 6-MP to its nucleotide but also the synthesis of guanosine 5'-monophosphate via the salvage pathway seems to be severely restricted. However, SL-1250 and SM-108 can be activated to their nucleotide even in these 6-MP-resistant cells because the activation of these compounds is proceeded by adenine phosphoribosyltransferase. In conclusion, suppression of de novo purine synthesis with SL-1250 and SM-108 seems to be a very efficient means of killing these 6-MP-resistant cells, which lack a salvage pathway for guanosine 5'-monophosphate. (Author abstract) (14 Refs)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

14. SINGLE AND SEQUENTIAL COMBINATION INTRAVESICAL CHEMOTHERAPY OF MURINE BLADDER CANCER.

Soloway MS, Nissenkorn I, McCallum LW, Murphy WM
956 Court St., Room 2H22, Memphis, TN, 38163
Urology; 19(2):169-175 1982

We investigated the effectiveness of intravesically administered drugs on the tumor incidence and tumor size in a FANFT-induced animal model for bladder cancer. In the first experiment 106 C3H/He mice were divided into a control and three treatment groups. Therapy consisted of either cis-diamminedichloroplatinum (II) (DDP), mitomycin C, or thiotepa (triethylene thiophosphoramide). There was a reduction in the tumor incidence in all treated groups; this was statistically significant for those receiving mitomycin C (p less than 0.04) and DDP (p less than 0.001). No significant difference in the mean or median tumor wt (an index of tumor volume) between the treated and control groups was found. In a second experiment intravesical combination chemotherapy was compared to single-agent therapy. Animals received either doxorubicin hydrochloride (Adriamycin), mitomycin C, thio-tepa, mitomycin C doxorubicin, or mitomycin C thio-tepa. Although there was no significant difference in tumor incidence among the groups with the exception of mice receiving thio-tepa, animals receiving sequential combination chemotherapy had lower mean and median bladder wt suggesting an improved therapeutic effect. (Author abstract) (24 Refs)

15. THE DRUG SENSITIVITY OF VP-16 IN VITRO IN BLADDER CANCER CELL LINES, KK-47, KW-103, AND RT4 AND IN RENAL CANCER CELL LINE, KN-41.

Hisazumi H, Nakajima K, Kuroda K
Dept. Urology, Sch. Medicine, Kanazawa Univ., Kanazawa, Japan
Hinyokika Kiyo; 27(7):771-774 1981

Using a colony formation technique and KK-47, KW-103 and RT4 cell lines established from human bladder transitional cell carcinomas and KN-41 cell line from a human renal cell carcinoma, the drug sensitivity of VP-16 was determined. The survival curves of the cell lines showed that this agent has a concentration dependent cell killing effect. From the drug sensitivity at 50% and 90% inhibitions (ID50 and ID90) determined from the survival curves in these cell lines at 2-and 24-hr exposure series of the drug, it was indicated that VP-16 has almost the same cell killing effects as those of bleomycin and cis-platinum. Compared with those of mitomycin C, adriamycin and carboquone, the ID50 and ID90 values of VP-16 were 1 to 3 digits higher in order. (Author abstract) (8 Refs) (In JPN)

16. CONTROL OF IN VIVO (CELLULAR) PHLEOMYCIN SENSITIVITY BY NUCLEAR GENOTYPE, GROWTH PHASE, AND METAL IONS.

Moore CW
Dept. Radiation Biology, Sch. Medicine and Dentistry, Univ. Rochester, Rochester, NY, 14642
Cancer Res; 42(3):929-933 1982

Nuclear genotype, growth phase, and the presence of metal ions all proved to be important in controlling the lethal effects of phleomycin in eukaryotic Saccharomyces cerevisiae. Among 120 normal and radiation-sensitive strains compared for their sensitivities to lethal effects of phleomycin, all mutant strains exhibiting enhanced sensitivities to phleomycin killing were also sensitive to killing by ionizing radiation. Mutants exhibiting sensitivities to phleomycin similar to normal strains of the same ploidy were sensitive to ultraviolet radiation. We conclude that cellular recovery from phleomycin-induced damage in yeast depends upon the function of some or all of 13 independent genes and upon at least some of the same steps in cellular pathways for the biological repair of damage by ionizing radiation. In this respect, the action of phleomycin is similar to the action of its structurally similar analog, bleomycin, even though phleomycin was substantially more cytotoxic. Stationary-phase haploid yeast cells were more sensitive than exponentially growing cells to killing by phleomycin. Survival of stationary-phase yeast was reduced to 0.3 -0.07% (S.E.) after 20-min exposures to phleomycin (1 ug/ml; approx 6.7 x 10(-7) M), but lethal effects of phleomycin were completely eradicated (98% survival) by the presence of 0.05 M ethylenediaminetetraacetate during the treatment period. The inactivation indicates an important role for one or more metal ion(s) in the in vivo toxicity of the phleomycin-bleomycin group of anticancer antibiotics. (Author abstract) (46 Refs)

17. EFFECTS OF HYPERTHERMIA AND ETHANOL ON THE CYTOTOXICITY OF BLEOMYCIN, ADRIAMYCIN, CIS-DIAMMINEDICHLOROPLATINUM(II) AND MACROMOMYCIN TOWARD HELA CELLS.

Ishida A, Mizuno S

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Gan; 73(1):129-131 1982

The cytotoxic effect of bleomycin on HeLa S3 cells is greatly enhanced when the cells are exposed to ethanol before drug treatment or treated with the drug at 43 C (hyperthermic temperature). On the other hand, the cytotoxic effects of adriamycin, cis-diamminedichloroplatinum(II) and macromomycin are not enhanced by ethanol exposure, but are potentiated by 43 C hyperthermia. This effect of ethanol suggests a unique mode of action in sensitizing cells to bleomycin. (Author abstract) (14 Refs)

18. COMBINATION CHEMOTHERAPY FOR THE 9L RAT BRAIN TUMOR MODEL SYSTEM.

Vats TS, Kimler BF, Henderson SD, Morantz RA

Dept. Pediatrics, Univ. Kansas Medical Center, Rainbow Blvd. at 39th St., Kansas City, KS, 66103

Cancer Treat Rep; 66(3):575-579 1982

Utilizing the 9L intracerebral rat brain tumor system, we have demonstrated that the combination of bleomycin delivered ic and BCNU (carmustine) given systemically is more therapeutically effective than either agent used alone. This benefit can be achieved without excessive short-term normal tissue damage. Furthermore, the potential for long-term normal tissue effects is reduced because of the low dose of bleomycin required. There was no difference between bleomycin given 16 hr before BCNU administration and the reverse sequence. These results suggest the possibility of adding intratumor bleomycin to protocols using BCNU for the treatment of malignant human brain tumors. (Author abstract) (8 Refs)

19. COMBINATION ANTITUMOR THERAPY WITH LENTINAN AND BACTERIAL LIPOPOLYSACCHARIDE AGAINST MURINE TUMORS.

Abe S, Yoshioka O, Masuko Y, Tsubouchi J, Kohno M, Nakajima H, Yamazaki M, Mizono D

Faculty Pharmaceutical Sciences, Teikyo Univ., Sagamiko-cho, Tsukui-gun, Kanagawa-ken 199-01, Japan

Gan; 73(1):91-96 1982

The antitumor effects of lentinan and bacterial lipopolysaccharide (LPS) were studied. Combined treatment with lentinan and LPS was very effective against Ehrlich carcinoma in ddY mice, and the syngeneic mammary carcinoma MM46 in C3H/He mice. Studies on the effective doses and times of administration showed that a single injection of lentinan plus LPS 12 days after subcutaneous inoculation of these tumors caused complete regression in 60 to approx 90% of the animals; complete regression of MM46 carcinoma was seen in 83% of the animals. (Author abstract) (19 Refs)

20. THE ROLE OF METHOTREXATE AND DIHYDROFOLATE POLYGLUTAMATES IN THE ENHANCEMENT OF FLUOROURACIL ACTION BY METHOTREXATE.

Fernandes DJ, Moroson BA, Bertino JR

Dept. Pharmacology, Yale Univ. Sch. medicine, New Haven, CT, 06510

Cancer Treat Rep; 65(Suppl1):29-35 1981

The effect of the methotrexate (MTX)-5-fluorouracil (FUra) combination on L1210 cell viability was highly sequence dependent in that a 1.4 log (25-fold) increase in cytotoxicity was observed when the MTX exposure preceded FUra, as compared to the reverse sequence. The formation of ternary complexes of thymidylate synthetase has been examined as a basis for the interaction of FUra and MTX in L1210 cells. L1210 cells converted 39% of the total intracellular MTX into MTX-poly-gamma-glutamates within 4 hr of a 1 uM MTX exposure. MTX-diglutamate (2,4-diamino,N(10)-methylpteroyldiglutamate) and MTX-triglutamate were the predominant metabolites. In contrast to the ternary complexes formed with MTX and MTX-diglutamate, the 5-fluorodeoxyuridylate (FdUMP)-7,8-dihydropteroylpentaglutamate-enzyme and the FdUMP-5,10-methylenetetrahydropteroylpentaglutamate enzyme and the FdUMP-5,10-methylenetetrahydropteroylpentaglutamate enzyme complexes were stable to polyacrylamide gel electrophoresis under nondenaturing conditions. MTX-diglutamate enhanced the extent of tight-binding inhibition of thymidylate synthetase activity by FdUMP in the presence of saturating 5,10-methylenetetrahydropteroylpentaglutamate, suggesting that MTX-diglutamate did not antagonize the formation of FdUMP-5,10-methylenetetrahydropteroylpentaglutamate enzyme complex. We propose that the sequence-dependent effect of MTX plus FUra on L1210 cell viability results from MTX and MTX polyglutamate inhibition of dihydrofolate reductase, and consequently a trapping of intracellular folates as dihydrofolate polyglutamates that could increase the extent of FdUMP binding to thymidylate synthetase. (Author abstract) (24 Refs)

21. INTERACTIONS BETWEEN MISONIDAZOLE AND HYPERTHERMIA IN EMT6 SPHEROIDS.

Morgan JE, Bleehen NM
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Br J Cancer; 44(6):810-818 1981

The effect of hypoxic misonidazole (MISO) pretreatment on the subsequent heat sensitivity of EMT6 multicellular tumor spheroids has been investigated. Spheroids were grown in static culture and treated when either 200-300 um or 650-800 um in diameter. Pretreatment was carried out in glass spinner vessels containing 100 ml medium with or without 5 mM MISO under conditions of hypoxia. Three-hr hypoxic pretreatment with 5 mM MISO significantly enhanced the subsequent response of 200 um spheroids to heat at 43 C. Oxic incubation at 37 C between pretreatment and heating caused progressive loss of heat sensitization with time, recovery being almost complete after 6 hr. Recovery was inhibited by incubation at 0 C during the interval. Preheating 200 um spheroids at 43 C for 2 hr increased their subsequent sensitivity to hypoxic MISO at 37 C. These results are discussed in relation to known mechanisms of MISO metabolism. (Author abstract) (13 Refs)

22. EFFECTS OF PIPERAZINEDIONE (NSC 135785) PLUS IRRADIATION ON ENDOGENOUS CFU-S, INTESTINAL CRYPTS, AND AS A POSSIBLE ABLATIVE PROTOCOL FOR MARROW TRANSPLANTATION AS EVALUATED IN RAUSCHER LEUKEMIC MICE.

Meredith RF, OKunewick JP, Kovacs CJ, Evans MJ, Dicke KA
Cancer Res. Lab., ASRC, Allegheny General Hosp., Pittsburgh, PA, 15212
Radiat Res; 89(3):559-574 1982

The potential usefulness of piperazinedione as a marrow ablative agent in transplantation therapy and the possible attendant risk of intestinal damage were examined in normal and Rauscher leukemic mice. When given in two doses prior to total-body irradiation (TBI), three different protocols of piperazinedione (0.2 or 0.3 mg/20-g mouse) significantly reduced survival of endogenous colony forming units in leukemic mouse spleens compared to TBI alone. Two of the three protocols had similar results in normal mice. Same day administration of piperazinedione and TBI to leukemic mice caused a large number of early deaths. Significant effects of piperazinedione and TBI on leukemic mouse intestine occurred when the drug was administered on the same day as TBI; however, negligible effects occurred when the drug was administered several days before TBI. Survival of leukemic mice given marrow transplantation after piperazinedione and TBI was significantly better than in mice given TBI alone, when the drug was administered 5 and 6 days prior to TBI and transplantation. Piperazinedione may be a useful drug for preparing leukemic recipients for marrow transplantation therapy. (34 Refs)

23. AN APPROACH TO THE USE OF POLYAMINE INHIBITORS FOR CANCER THERAPY.

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Med Biol; 59(5/6):458-461 1981

An approach to the use of polyamine biosynthesis inhibitors such as alpha-difluoromethylornithine (DFMO) in the treatment of brain tumors is described in terms of an idealized approach to reduction of cell numbers. Polyamine biosynthesis inhibitors are potentially useful for preventing regrowth of cells between steps in administration of other treatments because they are easily administered, minimally toxic to normal tissues, and inhibit cell proliferation. DFMO and other polyamine synthesis inhibitors may also potentiate the action of other agents, ie, they are biological response modifiers. Using the in vivo 9L rat brain tumor model, the therapeutic effect of DFMO and 1,3-bis(2-chloroethyl)-1-nitrosourea in combination was studied. The results were not conclusive, but additivity seems probable. The timing of biological response modifier administration is critical to the success of a therapy program, as illustrated by recent studies with cytosine arabinoside. (15 Refs)

24. HUMAN TUMOR XENOGRAFTS IN ATHYMIC (NUDE) MICE: CHEMOTHERAPY TRIALS IN SERIALLY TRANSPLANTED TUMORS.

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Ann Clin Lab Sci; 12(1):51-59 1982

In a total of 38 consecutive attempts at transplanting freshly excised malignant human neoplasms in athymic nu/nu mice during the past year, 12 resulted in successful xenografts. To date, all of these have been subsequently transplanted for two or more generations. These successful xenografts include two squamous cell carcinomas of the head and neck, three squamous cell carcinomas and one undiffer entiated large cell carcinoma of the lung, three adenocarcinomas of ovarian or endometrial origin, and one carcinoma of each of the following sites: urinary bladder, stomach, and colon. Chemotherapy trials on three different squamous cell carcinomas serially transplanted in nude mice revealed three different degrees of sensitivity to bleomycin. One tumor which was markedly sensitive to bleomycin showed only a slight response to cis-diamminedichloroplatinum (II). These chemotherapy trials will be expanded to wider panel of transplantable human squamous cell carcinomas of different origins with anti-tumor agents used singly or in combination. (Author abstract) (23 Refs)

25. ANTITUMORAL IMMUNOADJUVANTICITY OF PARIETAL SKELETONS OF CANDIDA ALBICANS AND MICROCOCCI.

Favalli C, Baccarini M, Blasi E, Bevilacqua R, Rinaldi C, Mastroviti F
Istituto di Microbiologia, Universita degli Studi di Roma, Roma, Italy
Boll Soc Ital Biol Sper; 57(18):1911-1915 1981

Antitumoral immunoadjuvanticities (IA) of Candida albicans (CA) and Micrococcus lysodeiticus (ML) were evaluated as follows. Parietal insoluble glucan fraction or glucan ghost (GG) was prepared from the CA after repeated extractions with alkalies and acids. Ascitic lymphoma LSTRA was induced in Balb/c mice CD2f1 by Maloney virus. The GG of the CA and the parietal skeletons (PS) of the ML were injected ip 14 days before or 1 day after the tumor transplantation (TT). Effect of the antiblastic agent carmustine (BCNU) was evaluated by administering it 5 days after the TT. Control tests were carried out with inactivated whole cells of the CA. The antitumoral effect was evaluated on the basis of median survival time (MST) and long term survival time (LST: 60 days after the TT), using the Mann-Whitney test. The MST was increased somewhat only with the whole cells of the CA; neither the GG nor the PS had any effect in the absence of the BCNU. The IA was evident in the presence of the BCNU, increasing with dosage (10.8, 18, and 30 mg/kg); this effect was most pronounced when whole cells of the CA were used, with MST of 16%, 30% and 60% and LST of 0%, 25%, and 56% respectively, for the increasing dosages of BCNU . (3 Refs) (In ITA)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

26. THE ROLE OF SOLUBLE FACTORS IN BLEOMYCIN-INDUCED PULMONARY FIBROSIS.

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Am J Pathol; 106(2):156-164 1982

Endotracheal administration of bleomycin causes pulmonary fibrosis characterized by increased collagen synthesis and deposition. Incubation of normal lung mince with neutral salt soluble extracts of lungs from normal and bleomycin-treated rats caused a dose-dependent inhibition of collagen and noncollagenous protein synthesis. Bleomycin-treated lung extracts, however, were significantly less eff ective in such inhibition when compared with normal lung extracts. This inhibitory activity was not diminished by dialysis in tubing with nominal mol wt cutoff of 10,000 but was destroyed by heat (70 C) and trypsin digestion. This inhibitory activity could not be ascribed to residual serum or bleomycin in the lung extracts. Fractionation on Sephacryl S-200 showed inhibitory activity to be heterogeneous with Mr (apparent mol wt) greater than 100,000. Extracts from spleen showed similar inhibitory activity but showed no difference in intensity between normal and bleomycin-treated spleen. These data suggest that loss or decrease in production of lung inhibitory regulatory factors is partly responsible for the noted increase in collagen production and deposition in bleomycin-induced pulmonary fibrosis. (Author abstract) (20 Refs)

27. ANTITUMOR ANTIBIOTICS I: ANTHRACYCLINES.

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Cancer Chemotherapy 1981- The EORTC Cancer Chemotherapy Annual 3. Pinedo HM, ed. Amsterdam, Excerpta Medica, 504 pp, 1981.

Mechanisms of action, pharmacokinetics, interaction with radiation, and cardiotoxicity of various anthracycline antitumor antibiotics are reviewed. Mechanisms of action include discussions of free radical formation via metabolic reduction, interaction with DNA, and membrane effects. Among analogs discussed are aclacinomycin A, nogalomycin and its analogs, and others such as AD-32, and the N,N-dialkyl analogs of adriamycin and daunorubicin. Over the past yr, greatest advances have been made in the mechanism of action, analog development, and cardiac toxicity. (77 Refs)

28. EVALUATION OF MISONIDAZOLE PERIPHERAL NEUROTOXICITY IN RATS BY ANALYSIS OF NERVE TRAINS EVOKED RESPONSE.

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Int J Radiat Oncol Biol Phys; 8(1):69-74 1982

Sensitivity of nerve train analysis (NTA) for the diagnosis of misonidazole (MS) peripheral neuropathy was studied in 24 Fischer 344 rats in a randomized, single blind study. An in vivo model was developed for the evaluation of the neurotoxicity of other radiosensitizing agents. The decrease in amplitude for control rats was never greater than 78%. Rats receiving low-dose MS (100 mg/kg/day) had amplitude changes similar to control rats. All rats receiving low-dose MS survived the study without marked change in amplitude of the compound action potential (CAP) 10 vs CAP 1. Rats treated with high-dose MS (300 mg/kg/day) showed a progressive decrease in the percent amplitude of CAP 10 vs 1. Two rats died within 48 hr of the third evaluation. At the high MS dose, no rats could be treated beyond day 18. Control and low-dose rats did not show any significant increase in percent latency throughout the study. Before death, rats treated with high-dose MS showed increases in the percent latency of CAP 10 vs 1. Linear regression analysis showed no statistically significant difference between control and low-dose rats. However, the percent decrease in amplitude for high-dose rats was significant. All rats (except one that died on day 18 and exhibited amplitude and latency abnormalities) treated with low-dose MS were histologically normal. All rats treated with high-dose MS demonstrated brain stem hemorrhages situated in the peri-fourth ventricular region. Microscopic evaluation demonstrated degeneration of the cochlear, lateral vestibular, and superior olivary nuclei. Peripheral nerves of these rats revealed a marked axonal loss and intermittent regions of demyelination. (24 Refs)

29. DECREASED CYTOTOXICITY OF CIS-DIAMMINEDICHLOROPLATINUM(II) BY ALPHA-DIFLUOROMETHYLORNITHINE DEPLETION OF POLYAMINES IN 9L RAT BRAIN TUMOR CELLS IN VITRO.

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Cancer Res; 42(4):1296-1299 1982

Before treatment with the cytotoxic drug cis-dichlorodiammineplatinum(II) (cis-platinum), 9L rat brain gliosarcoma cells grown in vitro were depleted of intracellular polyamines by alpha-difluoromethylornithine (DFMO; 10 mM, 48 hr), an enzyme-activated, irreversible inhibitor of the polyamine-synthetic enzyme ornithine decarboxylase. In contrast to studies that showed that the cytotoxicity of 1,3-bis (2-chloroethyl)-1-nitrosourea as measured by colony-forming efficiency is enhanced by DFMO depletion of intracellular polyamines, the cytotoxicity of cis-platinum was significantly decreased in polyamine-depleted 9L cells. At 10, 1, and 0.1% survival levels the dose modification factors were 2.0 to 2.1. Addition of exogenous putrescine to polyamine-depleted 9L cells 24 hr before treatment with cis-platinum partially reversed this phenomenon. When 9L cells were treated either with DFMO and cis-platinum or with DFMO, putrescine, and cis-platinum for 1 hr, a time period that is too short for DFMO to affect intracellular polyamine levels, the cytotoxicity of cis-platinum was decreased, but to a significantly lesser extent than by the 48 hr DFMO pretreatment. Putrescine alone did not alter the cytotoxic effect of cis-platinum when administered either 24 or 1 hr before treatment. DFMO appears to affect cis-platinum cytotoxicity by two different mechanisms, the first mediated through polyamine depletion and the second through a direct interaction with cis-platinum. (Author abstract) (29 Refs)

30. EFFECTS OF FLUORODEOXYURIDINE ON THE DEVELOPING INNER EAR OF THE RAT.

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Dept. Anatomy, Mount Sinai Sch. Medicine City Univ. New York, New York, NY, 10029
Anat Rec; 202(3):359-370 1982

The inner ear in rats develops from the surface ectoderm on Day 8 of a 22-day gestational period. Labeled thymidine incorporation studies have indicated that in the developing inner ear most of the cells undergo terminal mitosis between gestational Days 13 and 15. During this period the developing inner ear would be particularly vulnerable to environmental hazards. To test this hypothesis, pregnant rats were given a single ip injection of 5-fluoro-2'-deoxyuridine (FUdR), an antimitotic substance, on gestational Days 12 to 16. The rats also received one injection of 3H-thymidine 1 hr prior to the removal of the fetuses. The animals were killed after various time intervals following the treatment, and the otocysts or inner ears were prepared for morphologic observations and biochemical assays. The cells in the inner ear of rats exposed to FUdR exhibited pyknotic nuclei and chromatolytic degeneration, and they eventually died. By 4 hr after the administration of FUdR, pyknotic nuclei were seen in the antiluminal zone of the otic epithelium, and there was a substantial decrease in the number of the otic cells. This decline in cell number was seen until 24 hr after treatment. However, the inner ears from the fetuses exposed to FUdR during gestational Days 12-15 showed complete recovery from the toxic effects of the drug when examined on Day 21 of gestation. The phenomenon of programmed cell death observed in the developing inner ear of the rat indicates that more cells are produced during the earlier stages of development than are required for the definitive adult structures. This phenomenon may represent an important protective feature. The redundant production of cells perhaps allows the developing otocyst to respond to an environmental stress by subtotal destruction of cells from the pool of undifferentiated cells, resulting in relatively fewer congenital anomalies of the inner ear. (Author abstract) (22 Refs)

31. INACTIVATION OF ULTRAVIOLET REPAIR IN NORMAL AND XERODERMA PIGMENTOSUM CELLS BY METHYL METHANESULFONATE.

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Cancer Res; 42(3):860-863 1982

Excision repair of ultraviolet damage in the DNA of normal and xeroderma pigmentosum (Groups C, D and variant) cells was inactivated by exposure of cells to methyl methanesulfonate immediately before irradiation independent of the presence of 0 to 10% fetal calf serum. The inactivation could be represented by a semilog relationship between the amount of repair and methyl methanesulfonate concentration up to approx 5 mM. The inactivation can be considered to occur as the result of alkylation of a large (about 10(6) daltons) repair enzyme complex, and the dose required to reduce repair to 37% for most cell types was between 4 and 7 mM. No consistent, large difference in sensitivity to methyl methanesulfonate was found in any xeroderma pigmentosum complementation group compared to normal cells, implying that reduced repair in these groups may be caused by small inherited changes in the amino acid composition (ie, point mutations or small deletions) rather than by losses of major components of the repair enzyme complex. (Author abstract) (19 Refs)

32. COMBINED EFFECTS OF VINBLASTINE AND VINCRISTINE ON MOUSE HEPATOCYTES WITH RESPECT TO ULTRASTRUCTURAL ELEMENTS.

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Exp Pathol; 20(3):163-174 1981

The results of a single dose of the microtubule-destroying agents vinblastine/vincristine (0.5 mg/0.5 mg) on the ultrastructural elements of mouse hepatocytes was studied using the techniques of thin-sectioning and freeze-fracture following intravenous injection of the drugs. Several cytoplasmic modifications were observed in the hepatocytes. These included the storage of lipid droplets, a heavy accumulation of autophagosomes and vacuoles with very low density lipoprotein (VLDL)-like vesicles, large glycogen fields and dilated intercellular spaces with intrahepatocytic vacuoles. The rough endoplasmic reticulum exhibited pathological changes with loss of ribosomes and the bile canaliculi exhibited in some cases the loss of microvilli as well as dilatation of the lumen. The tight junctions surrounding the bile canaliculi exhibited alterations as well. The strands were reduced in number and showed a less organized arrangement. The gap junctions showed an increase in size as well as an irregular outline in contrast to controls. These findings are interpreted as non-specific toxic phenomena. However, the possibility cannot be precluded that certain phenomena, such as alterations in the cell junctions, may be attributable to specific microtubule-destroying properties of the drugs. (Author abstract) (61 Refs)

33. EFFECT OF PHENOBARBITAL ON THE TOXICITY AND ANTITUMOR ACTIVITY OF DIBROMODULCITOL AND DIANHYDROGALACTITOL.

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Arzneim Forsch; 32(2):149-151 1982

Pretreatment with 5-Ethyl-5-phenylhexahydropyrimidin-2,4,6-trione (phenobarbital) significantly decreased the acute toxicity of 1,6-dibromo-1,6-dideoxygalactitol (dibromodulcitol) in H/Riop-Swiss mice and Wistar rats. Toxicity of dianhydrogalactitol, however, was not influenced to a considerable measure. Phenobarbital did not alter in itself the growth rate of the tumors examined. It significantly reduced, however, the antitumor activity of dibromodulcitol in NK/Ly-mouse lymphoma and Yoshida rat tumor. In contrast, the cytostatic effect of dianhydrogalactitol was not influenced at all by phenobarbital. The dissimilar effects of phenobarbital on the toxicity and antitumor activity of dibromodulcitol and dianhydrogalactitol are probably due to differences both in their metabolism and pharmacodynamics. (Author abstract) (21 Refs)

34. CIRCADIAN STAGE DEPENDENCE OF CIS-DIAMMINEDICHLOROPLATINUM LETHAL TOXICITY IN RATS.

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Cancer Res; 42(3):945-949 1982

Renal physiology is circadian rhythmic. The major toxicity of cis-diamminedichloroplatinum (cisplatin) is irreversible renal damage. A single dose of cisplatin (11 mg/kg) was given to groups of standardized female Fischer 344 rats at one of six equispaced circadian stages. A statistically significant effect of time of injection upon tolerance was found by chi2 analysis. Differences of three- to eight-fold in survival rate at 50% mortality and a nearly three-fold difference in long-term survival depen on circadian timing of cisplatin administration. Cisplatin timing resulting in optimal tolerance was similar from study to study. Additional 0.9% NaCl solution was administered with cisplatin in three experiments and resulted in an increase in overall mean survival time. It also resulted in an amplification of the survival rhythm without changing its timing. The increase in survival resulting from 0.9% NaCl solution loading, when compared to controls receiving cisplatin alone, was also highly time dependent. A 52% improvement in mean survival time was achieved in those animals receiving cisplatin and 0.9% NaCl solution at the most favorable circadian stage, as compared to a 20% improvement when this regimen was administered at an inopportune circadian stage. The safest time for cisplatin administration is near the midactivity span, shortly after the max of the circadian rhythm in rectal temperature. (Author abstract) (26 Refs)

35. REDUCTION OF CIS-DIAMMINEDICHLOROPLATINUM NEPHROTOXICITY IN RATS BY OPTIMAL CIRCADIAN DRUG TIMING.

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Cancer Res; 42(3):950-955 1982

A prominent circadian rhythm in the nephrotoxicity of a therapeutic dose of cis-diamminedichloroplatinum (cisplatin) is demonstrated in female Fischer rats. Rats were randomized to receive two doses of either cisplatin or 0.9% NaCl solution 14 days apart at the times of either high or low values in their circadian rhythm of urinary volume. Toxicity was assessed by measuring changes in body wt and changes in the 24-hr means of urinary volume, blood urea nitrogen, and urinary beta-N-acetylglucosaminidase (NAG) activity. Toxicity was least in rats which received the drug near the circadian max of urinary volume. Conversely, rats which received the same dose of drug near the circadian minimum of urinary volume lost more wt and exhibited a two-fold increase in the 24-hr mean of urinary volume, a three-fold rise in the 24-hr mean of blood urea nitrogen, and a five fold increase in the 24-hr mean of urinary NAG activity. A positive correlation between urinary NAG at the time of cisplatin administration and the extent of cisplatin nephrotoxicity was demonstrated (p less than 0.02). A correlation also was found between tissue NAG concentration and tissue uptake of cisplatin (p less than 0.001). A marked circadian rhythm of NAG activity in proximal tubular cells may contribute to the prominent circadian rhythm in murine renal tolerance for cisplatin. (Author abstract) (37 Refs)

PHARMACOKINETICS OF ANTITUMOR AGENTS

36. PLASMA AND TISSUE DISTRIBUTION OF MISONIDAZOLE (RO 07-0582) IN THE RAT BEARING A CHEMICALLY-INDUCED TUMOR.

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J Pharmacol; 12(4):383-391 1981

Plasma and tissue distribution of misonidazole (MS) was determined in male Wistar rats bearing nickel sulfate-induced rhabdomyosarcomas following ip injection of MS (25 mg/100 g). Rapid diffusion of MS into plasma and tissue was observed. Peak plasma MS concentrations were observed at the end of 10-30 min; at the same time, maximal concentrations were detected in muscles, brain, tumor, liver, and kidney. MS concentrations in the muscle, brain, tumor, liver and kidney were 50%, 47%, 36%, 8%, and 13%, respectively, of that of plasma concentration. No significant differences were observed between MS concentrations in central (32%) and peripheral (36%) regions. Slow elimination of MS from the hypoxic tumor was demonstrated. Half life of MS in the tumor periphery was 52 min as compared with 235 min in central regions, and for liver and renal 55 min and 36 min,respectively. (20 Refs) (In FRE)

37. ENHANCED LYMPH NODE UPTAKE OF MELPHALAN FOLLOWING LIPOSOMAL ENTRAPMENT AND EFFECTS ON LYMPH NODE METASTASIS IN RATS.

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Cancer Treat Rep; 66(3):517-527 1982

The effect of liposomal entrapment of melphalan (MPL) on its tissue distribution and activity against experimental lymph node metastasis was evaluated in rats. MPL appears to associate with the lipid phase of liposomes; entrapped MPL was not hydrolyzed and was gradually released from lipo somes during incubation at 37 C. Free [14C]MPL injected sc into the thigh of rats was rapidly cleared from the injection site, with only 0.6% of the 14C activity remaining after 2 hr. The concentration of MPL in the ipsilateral inguinal lymph nodes showed a transient increase over that in contralateral nodes at 0.5 hr, although MPL concentrations were similar in ipsilateral and contralateral nodes at 1 hr. After sc injection of [14C]MPL/[3H]PC-liposomes, about 4% of the 14C activity was present at the injection site at 2 hr after treatment. The concentration of phosphatidylcholine equivalents in ipsilateral lymph nodes was at least 50x higher than that in plasma, lung, or contralateral lymph nodes at all time intervals examined. Similarly, liposomal entrapment of MPL enhanced its uptake by ipsilateral lymph nodes. Rats were inoculated sc in the calf with a tumor brei, the leg was amputated 10 days after inoculation and animals were treated on day 13 with free or liposome-entrapped MPL injected sc into the thigh. Liposome-entrapped MPL produced a greater reduction in the wt of lymph node metastases as compared with free MPL. Thus, when MPL was entrapped in liposomes, a dose of 0.125 mg/kg reduced the wt of lymph node metastases to about 50% that in controls. A dose of 0.5-1.0 mg/kg was required to exert an equivalent effect on lymph node tumor growth when free MPL was administered. These results suggest that the interstitial injection of liposomes containing MPL may be useful for the postoperative treatment of lymph node metastases. (25 Refs)

38. STUDIES ON THE PHARMACOKINETICS AND METABOLISM OF CIS-DICHLORO-TRANS-DIHYDROXY-BIS-ISOPROPYLAMINE PLATINUM (IV) IN THE DOG.

Pendyala L, Cowens JW, Creaven PJ
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Cancer Treat Rep; 66(3):509-516 1982

A new antineoplastic platinum compound, cis-dichloro-trans-dihydroxy-bis-isopropylamine platinum(IV) (CHIP), was administered iv to dogs at a dose of 10 mg/kg. Thin-layer chromatography and high-pressure liquid chromatography (HPLC) were used to evaluate the pharmacokinetics of total Pt and of unchanged drug separated from the metabolites in urine. Both chromatographic procedures indicated a half-life of 0.3-0.5 hr for the unchanged CHIP (based on urinary excretion rates). Decay of total Pt after administration of CHIP was biphasic, with an alpha-half-life of 0.6 hr and a beta-half-life of 39.4 hr. The long beta-half-life thus appears to be due to the retention of metabolites. Unchanged CHIP was separated from two groups of more polar Pt-containing metabolites by HPLC, as well as from another less polar Pt-containing complex that is found in urine of untreated dogs to which CHIP was added. After the administration of CHI P, with the simultaneous decline in its level, the proportion of the very polar Pt-containing metabolite(s) accumulated in the dog urine. Unlike cisplatin, CHIP did not bind to plasma proteins in vitro. (Author abstract) (26 Refs)

39. THE BINDING OF PLATINUM ETHYLENEDIAMINE DICHLORIDE TO PROTEINS, IN VITRO AND IN VIVO.

Robins AB
Dept. Radiopharmacology, Inst. Cancer Res., Sutton, Surrey, England
Chem Biol Interact; 38(3):349-356 1982

The binding to proteins of platinum ethylenediamine dichloride (PtenCl2) labeled with carbon-14 has been studied in vitro and in vivo. The metal complex binds to proteins in plasma with a half-time of about 1 hr and is distributed over all protein classes. At pharmacologically relevant levels the binding of platinum does not affect the biological function of the protein, eg, the immunoglobulins. Although the in vitro toxicity of PtenCl2 is decreased by binding to the proteins of the culture medium, it has not yet proved possible to determine whether binding in vivo, eg to tumor cytosol proteins. leads to loss in toxicity and whether it is reversible. (Author abstract) (15 Refs)

40. COMPARISON OF LYMPHATIC UPTAKE, METABOLISM, EXCRETION, AND BIODISTRIBUTION OF FREE AND LIPOSOME-ENTRAPPED [14C]CYTOSINE BETA-D-ARABINOFURANOSIDE FOLLOWING INTRAPERITONEAL ADMINISTRATION TO RATS.

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Drug Metab Dispos; 10(1):40-46 1982

Free [14C]cytosine beta-D-arabinofuranoside ([14C]ara-C) was completely absorbed from the peritoneal cavity of thoracic duct-cannulated rats by 6 hr after ip dosing. 14C levels in most tissues were higher at 4 hr than at 12 hr after dosing and were generally undetectable at 24 hr. By 6 hr after treatment only 2% of the dose was recovered in lymph, whereas 90% had been excreted in urine. Liposome entrapment of ara-C reduced the rates at which the drug was absorbed from the peritoneal cavity and excreted in urine while enhancing lymphatic uptake of the drug by more than 10-fold. Radioactivity in plasma and most tissues achieved higher concentrations and persisted for longer periods in rats given liposome-entrapped ara-C than in rats receiving the free drug. Most striking was the localization of 14C-activity in renal and thoracic lymph nodes of rats given liposome-entrapped ara-C, with 300 to 1,000-fold higher levels present at 4, 12, and 24 hr after dosing than in corresponding lymph nodes of rats receiving the free drug. The metabolic conversion of ara-C to uracil beta-D-arabinofuranoside (ara-U) was reduced by approximately three-fold following liposome entrapment of the drug. The enhanced lymphatic uptake and the localization and persistance of ara-C in lymph nodes resulting from liposome entrapment of the drug may be of benefit in treating tumors that metastasize via lymphatic pathways. (Author abstract) (46 Refs)

41. IDENTIFICATION OF THE PRINCIPAL BILIARY METABOLITE OF 4'-(9-ACRIDINYLAMINO)METHANESULFON-M-ANISIDIDE IN RATS.

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Drug Metab Dispos; 10(1):35-39 1982

m-AMSA [4'-(9-acridinylamino)methanesulfon-m-anisidide] labeled in either the acridine or anilino portion was used to investigate the disposition of this antitumor agent in rats. The principal biliary metabolite, which accounts for approximately 80% of the total biliary radioactivity for 90 min after administration and greater than 50% of the administered dose by 180 min after administration, had both the acridine and the anilino portions intact. Isolation and purification of the principal metabolite was achieved by preparative thin-layer chromatography on silica gel and column chromatography on Amberlite XAD-2 resin. A nuclear magnetic resonance (NMR) spectrum of the DCI salt in D_2O showed that the metabolite is the m-AMSA-glutathione conjugate in which the thioether linkage occurs at the 5'-position of the anilino ring. Synthesis of the metabolite was achieved by oxidizing m-AMSA with active MnO_2 to -methanesulfonyl- -(9-acridinyl)-3'-methoxy-2',5'-cyclohexadiene-1',4' diimine (m-AQDI) followed by reaction of m-AQDI with glutathione. The 1H-NMR spectrum of the synthetic product proved identical with that of the isolated metabolite. The demonstration that the principal biliary metabolite of m-AMSA involves glutathione bound to the 9-anilino ring suggests that m-AMSA may be bioactivated in vivo to the quinoidal diimine, m-AQDI. (Author abstract) (15 Refs)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

42. SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 4-(D-ALANYLAMINO)-2-AMINO-2,3,4-TRIDEOXY-L-THREO PENTOSE (3-DEOXYPRUMYCIN).

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Carbohydr Res; 99(1):59-69 1982

Three analogs of prumycin [4-(D-alanylamino)-2-amino-2,4-dideoxy-L-arabinose], ie, the 3-deoxygenated (1), that having the 2-amino and 3-hydroxyl groups interchanged (2), and that having C-2 deaminated (3), were synthesized. Examination of the antifungal and antileukemic activities showed that, for 1, the former activity was more potent against some fungi, whereas the latter was slightly weaker, than that of prumycin. (Author abstract) (12 Refs)

43. ISOLATION AND IDENTIFICATION OF THE ALKALOIDS FROM ANCISTROCLADUS TECTORIUS.

Chen Z, Wang B, Qin K, Zhang B, Su Q, Lin Q
Shanghai Inst. Materia Medica, Chinese Acad. Sciences, Shanghai, People's Republic of China
Yaoxue Xuebao; 16(7):519-523 1981

During the screening of plants for antitumor constituents, the crude alkaloid extracted from twigs and stems of Ancistrocladus tectorius with the aid of 95% ethanol was found to have an inhibitory effect on Walker 256 tumor in rats. To determine the active component, the free bases present in the crude alkaloid preparation were extracted with ether, the ether was removed, and the preparation was then chromatographed on an alkaline silica gel column, using chloroform: methanol (30:1 and 20:1) as the eluant; three crystalline fractions were thereby obtained. Recrystallization yielded pure crystalline products I, II, and III. Using standard chemical and physical methods (elemental analysis; mass spectrometry; IR, UV, and NMR spectroscopy), I and II were identified as ancistrocladine and hamatine, respectively (both known alkaloids), while III was determined to be a new alkaloid, 5-(4,5-dimethoxy-2-methylnaphthyl)-1,2,3,4-tetrahydro 6-hydroxy-8-methoxy-1,3-dimethylisoquinoline, and was named ancistrocline. NMR spectral data showed the 1-and 3-methyl groups in ancistrocline to be equatorial. The antitumor activities of the total alkaloids and of the fractions I and II were weak against murine S-180 and Ehrlich ascites tumors. (7 Refs) (In CHI)

44. STUDIES ON THE WATER-SOLUBLE CONSTITUENTS OF LICHENS. IV. EFFECT OF ANTITUMOR LICHEN-GLUCANS AND RELATED DERIVATIVES ON THE PHAGOCYTIC ACTIVITY OF THE RETICULOENDOTHELIAL SYSTEM IN MICE.

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Faculty Pharmaceutical Sciences, Kanazawa Univ., 13-1 Takara-machi, Kanazawa 920, Japan
Chem Pharm Bull (Tokyo); 29(11):3407-3410 1981

The phagocytic response of the mouse reticuloendothelial system (RES) was determined by carbon clearance assay after ip injection of the following lichen-derived polysaccharides: partially O-acetylated pustulan-type beta-D-glucan from Gyrophora esculenta Miyoshi (GE-3); lichenan-type beta-D-glucan from Usnea rubescens Stirt (UR-1-1); O-lauroylated derivatives of G-3, having lauroyl contents of 3.3, 12.0, and 42.2% (GE-3-L; lots 3, 4, and 7, respectively); and an O-carboxymethyl derivative of GE-3 (CM-GE-3). GE-3 seemed to stimulate the mouse RES in a dose-responsive way, with a single dose of 100 mg/kg resulting in a response equivalent to that with 50 mg/kg zymosan. UR-1-1 was ineffective; lipophilic (GE-3-L; 3, 4, 7) and hydrophilic (CM-GE-3) substitution yielded carbon clearance activities well below those of the unsubstituted glucan. The antitumor activity of UR-1-1 cannot be explained in terms of RES stimulation, and experiments to date have not succeeded in relating RES-stimulating activity of acetylated pustulan-type glucans to their antitumor effects. (26 Refs)

45. A NEW CLASS OF NITROSOUREAS. II. SYNTHESIS AND ANTITUMOR ACTIVITY OF 1-(2-CHLORETHYL)-3,3-DISUBSTITUTED-1-NITROSOUREAS HAVING A GLUCOPYRANOSYL, MANNO PYRANOSYL OR GALACTOPYRANOSYL MOIETY.

Tsujihara K, Ozeki M, Morikawa T, Taga N, Miyazaki M, Kawamori M, Arai Y
Res. Laboratories, Tanabe Seiyaku Co., Ltd., 2-2-50, Kawagishi, Toda-shi, Saitama 335, Japan
Chem Pharm Bull (Tokyo); 29(11):3262-3273 1981

Synthesis and characteristics of 42 aldohexose derivatives of nitrosoureas are described, and chemical and infrared and nuclear magnetic resonance spectral data for these compounds are presented. The glycopyranosylnitrosoureas (GPNUS) were tested for antitumor activity against leukemia L1210 and Ehrlich ascites carcinoma cells injected ip into BDF1 and ICR mice, respectively. Many of the compounds showed superior antitumor activity when compared to the positive controls: 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), 3[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2 chloroethyl)-1-nitrosourea (ACNU), and 1-(2-chloroethyl)-3-(beta-D-glucopyranosyl)-1 nitrosourea (GANU) in the same systems. The galactopyranosyl moiety is apparently the most effective in enhancing entry of the drug into cells. The other substituent on the N-3 position is also important in the antitumor activity; optimal activity occurs with compounds bearing an alkyl or alkenyl group with three or four C atoms, with much less activity if the alkyl group is larger. Alkyl groups with ether linkage were also effective substituents. Three of the GPNUS had 4-11x greater therapeutic ratios than those of CCNU, ACNU, and GANU against L1210, yet were less toxic than CCNU or ACNU. Acetylation of the hydroxyl group in the sugar moiety resulted in a marked decrease in antitumor activity against L1210. (10 Refs)

46. RING-HYDROXYLATED ANALOGUES OF LUCANTHONE AS ANTITUMOR AGENTS.

Archer S, Miller KJ, Rej R, Periana C, Fricker L
Chemistry Dept., Cogswell Lab., Rensselaer Polytechnic Inst., Troy, NY, 12181
J Med Chem; 25(3):220-227 1982

A series of ring-alkoxylated and ring-hydroxylated analogues of lucathone was prepared and tested for antitumor activity. The most biologically interesting members of this group were the 7-hydroxylucanthone derivatives, 50 and 51, which gave T/C values in the NCI P-388 antitumor screen of 188 and 265, respectively. The apparent association constants and deltaTm values for a number of analogue-DNA complexes were determined to ascertain whether there was any quantitative correlation with biological activity. The most that can be said is that intercalation may be a necessary but far from sufficient condition of antitumor activity. (Author abstract) (20 Refs)

47. NEW SUBSTANCES WITH CYTOTOXIC AND ANTITUMOR EFFECTS. IV. IN VITRO EFFECT OF SOME VERATRUM ALKALOIDS AND THEIR DERIVATIVES ON LEUKEMIA P388 CELLS.

Fuska J, Fuskova A, Vassova A, Voticky Z
Dept. Environmental Chemistry and Technology, Slovak Technical Univ., 880 37 Bratislava, Czechoslovakia
Neoplasma; 28(6):709-714 1981

Some Veratrum alkaloids and their derivatives exhibited an in vitro cytotoxic effect on leukemia P388 cells, depending on the structure of the skeleton of the molecule, particularly on the type of the heterocycle attached to C-20. Veracintine and 20-(2-methyl-1-pyrrolin-5-yl)-4-pregnen-3-one, which proved to be the most effective, inhibited incorporation of uridine, and to a lesser extent that of L-valine into P388 cells fractions. After a brief reaction (15 min), these substances became irreversibly bound in the P388 cells and stopped their further in vitro proliferation. The cytotoxic effect of veracintine became enhanced by sublethal doses of tubercidine (phase of max lethality at G1). (Author abstract) (12 Refs)

48. ANTITUMOR ACTIVITY OF ALKYLDISULFIDE DERIVATIVES OF 6-MERCAPTOPURINES AGAINST L-1210 LEUKEMIA.

Inomata M, Fukuoka F, Hoshi A, Kuretani K, Saneyoshi M
Natl. Cancer Center Res. Inst., 5-1-1, Tsukiji, Chuo-ku, Tokyo 104, Japan
J Pharmacobio Dyn; 4(12):928-932 1981

Antileukemic activity of a series of 14 6-mercaptopurine (6MP) and 15 6-thioguanine (6TG) derivatives was examined using male BDF1 mice inoculated with L-1210 cells (10(5) cells, ip). Doses ranged from 1-200 mg/kg daily (6MP) or 0.1-60 mg/kg daily (6TG). The same compounds were also administered po at doses of 10 mg/kg/day (6MP) and 1-60 mg/kg/day (6TG). Antitumor activity was determined by the increase in life span (ILS) over controls (ILS = Treatment/Control% - 100) and by therapeutic ratio (dose yielding 30% increase in ILS/optimal dose). Therapeutic ratio of 6TG given po was 8.1 versus 5.0 for ip injection, but that of 6MP was less po (3.2 versus 6.2). All derivatives tested yielded ILS greater than 30%. No derivatives were superior overall to the original agents. Therapeutic ratios of derivatives of these agents were decreased by oral administration though they were effective by ip injection. (5 Refs)

49. QUANTITATIVE DETERMINATION OF THE ACTIVE PRINCIPLES - ETHOXYSANGUINARINE AND ETHOXYCHELERYTHRINATINE IN MACLEAYA CORDATA (WILLD.) R. BROWN.

Cao L, Wang Z
Inst. Materia Medica, Academia Sinica, Shanghai, People's Republic of China
Yaowu Fenxi Zazhi; 1(5):296-299 1981

Ethoxysanguinarine (ES) and ethoxychelerythrinatine (EC) isolated from Macleaya cordata have been shown to be active against cervix cancer and thyroid tumors. A colorimetric method for the individual determination of ES and EC in a mixture of the two alkaloids is described. This method is based on different color reactions of the two alkaloids with acetic acid, and the resulting different absorption maxima: ES (red, 472 nanometer) and EC (yellow, 403 nanometer). (3 Refs) (In CHI)

50. THE ANTITUMOR AND MAMMALIAN XANTHINE OXIDASE INHIBITORY ACTIVITY OF 5-METHYL-6-SUBSTITUTED PYRROLO(2,3-D)PYRIMIDINE-2,4-DIONES.

Betlach CJ, Sowell JW
Massachusetts Coll. Pharmacy and Allied Health Sciences, Boston, MA, 02115
J Pharm Sci; 71(2):269-270 1982

The compound 5,6-dimethylpyrrolo(2,3-d)-pyrimidine-2,4-dione, which inhibits xanthine oxidase, was tested in vivo against two transplantable mouse lymphoid tumor systems (H-5 ascites tumor and L-1210 leukemia). Response to ip administration indicated the compound produced a toxic response, although none of the control mice died from similar doses. (4 Refs)

51. CANCER CURE?

Shapiro HA
No affiliation given
S Afr Cancer Bull; 25(4):171,172 1981

A substance sold under the trade name Nathpo by a South African layman was identified as a preparation of tannin. Because Nathpo has been advertized as a remedy for cancer and other diseases, it was tested for cytotoxicity. The preparation was equally cytotoxic to normal and tumor cells. Further tests of cytotoxicity and the toxicology of biologic tannins in humans are in progress. (no Refs)

STUDIES OF ANTIMETASTATIC AGENTS

52. CANCER CELL PROCOAGULANT: A NOVEL VITAMIN K-DEPENDENT ACTIVITY.

Delaini F, Colucci M, De Bellis Vitti G, Locati D, Poggi A, Semeraro N, Donati MB
Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea, 62, 20157 Milan, Italy
Thromb Res; 24(3):263-266 1981

Further elaboration of the unexplained, vitamin K-deficiency related, reducing metastasis of 3LL tumors was reported. Four sets of C57Bl/6J mice, the original source of the 3LL tumor, were used and all given 3LL-cell leg implants at day 0: 1. control with neomycin-supplemented diet, 2. as in 1. but diet deficient in vitamin K, and initiated 7 days before day 0, 3. warfarin present in drinking water from day 7, 4. as in 3. but vitamin K3 also in the water from day 14. All animals were sacrificed on day 17 and the primary tumor cells harvested. The tumor cell procoagulant activity (innate ability of 3LL cells to directly activate coagulation factor X) and thrombotest result were both 2. = 3. much less than 1. = 4. Since it had already been suggested that activated factor X might be responsible for fibrin deposition and thus contribute to metastasis, it was now suggested that the antimetastatic role of warfarin be reevaluated. (8 Refs)

INTERFERON AND OTHER ANTIVIRALS

53. EFFECTS OF N-BUTYRATE ON EPSTEIN-BARR VIRUS-CARRYING LYMPHOMA LINES.

Anisimova E, Saemundsen AK, Roubal J, Vonka V, Klein G
(c/o Saemundsen) Dept. Tumor Biology, Karolinska Institutet, S104 01 Stockholm, Sweden
J Gen Virol; 58(part1):163-171 1982

The compound n-butyrate has been shown to induce Epstein-Barr virus (EBV) antigen synthesis in certain EBV-carrying lymphoma lines. We have studied the effect of n-butyrate on two EBV -positive Burkitt lymphoma lines by immunofluorescence and electron microscopy. In the producer line P3HR-1, the drug induced not only early antigen (EA) and virus capsid antigen (VCA) synthesis, as shown before, but also increased the number of cells containing virus particles. The transition from VCA expression to the formation of virus particles was much more effective in treated cells than in EBV antigen-producing cells of the same line. The productive cycle was associated with the development of characteristic morphological changes. In the non-producer Raji cells, n-butyrate induced EA in only a minor fraction of the cells. There were, however, clear signs of differentiation in the direction of plasma cells. Two days after the addition of n-butyrate 80% of the Raji cells could be classified as plasmablasts. After 72 hr, 20% of the cells appeared as typical plasma cells. (Author abstract) (33 Refs)

54. ANTITUMOR EFFECT OF COMBINED INTERFERON AND HYPERTHERMIA IN MICE.

Yerushalmi A, Tovey MG, Gresser I
Radiation Unit, Weizmann Inst. Science, Rehovot, Israel
Proc Soc Exp Biol Med; 169(3):413-415 1982

The effect of hyperthermia and interferon (INF) was tested in C57B1/6 mice bearing transplantable Lewis lung carcinoma. Combined therapy with either exogenous INF or INF inducers (polyinosinic-polycytidylic acid or Newcastle disease virus) together with local hyperthermia had a greater antitumor effect than either treatment alone. (15 Refs)

55. PREVENTION OF INTERFERON-INDUCED AUGMENTATION OF CELLULAR ANTITUMOR EFFECTOR MECHANISMS BY PHORBOL ESTERS.

Keller R, Aguet M, Tovey M, Stitz L
Immunobiology Res. Group, Inst. Immunology and Virology, Univ. Zurich, Schonleinstrasse 22, CH-8032 Zurich, Switzerland
Cancer Res; 42(4):1468-1472 1982

Both natural killer cell- and macrophage-mediated spontaneous in vitro cytotoxicity for tumor targets is rapidly and strongly augmented by interferon. Macrophage-activating lymphokines considerably enhance macrophage-tumoricidal activity but did not affect natural killer cell-type cytotoxicity. Augmentation of cytolytic capacity by interferon and by macrophage-activating lymphokines is prevented by the tumor-promoting phorbol ester, 12-O-tetradecanoylphorbol-13-acetate. However, the classical antiviral activity and the specific binding of interferon to cell surface receptors remains unaffected by 12-O-tetradecanoylphorbol-13-acetate. (Author abstract) (27 Refs)

56. DIFFERENT SUSCEPTIBILITIES OF CULTURED MOUSE CELL LINES TO MOUSE INTERFERON.

Tsuruo T, Iida H, Tsukagoshi S, Oku T, Kishida T
Center Chemotherapy Center, Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan
Gan; 73(1):42-47 1982

Cultured mouse cells were treated with 3.3 to approx 10,000 units of mouse interferon for 3 days and further cultivated in fresh medium for 2 days (recovery incubation). The IC50 (concentration of drug required for 50% inhibition) of interferon was not changed much after the recovery incubation. The most susceptible cell line to interferon was B16 melanoma; the IC50 was 10.5 units per ml of medium on day 3 after the start of treatment. P388 leukemic cells, Lewis lung carcinoma cells, and colon adenocarcinoma 38 cells were moderately susceptible to interferon and the IC50s of these cell lines were 200, 80, and 180 units per ml medium, respectively, on day 3. The cells least susceptible to interferon were those of colon adenocarcinoma 26; IC50 was greater than 10,000 units per ml. In the recovery incubation, the growth of B16 melanoma cells, P388 leukemic cells, Lewis lung carcinoma cells and colon adenocarcinoma 38 cells was considerably inhibited when these cells were treated with more than 100 to approx 1,000 units of interferon per ml medium. The rate of multiplication was usually more than 1 for these cell lines, except for Lewis lung carcinoma cells where the rate of multiplication was less than 1. This indicates that interferon is not cytocidal towards B16 melanoma cells, P388 leukemic cells, or colon adenocarcinoma 38 cells, but mouse interferon is cytocidal towards Lewis lung carcinoma cells when the cells were treated with a relatively high concentration of interferon and then cultured in the medium without interferon. (Author abstract) (23 Refs)

57. LOW LEVELS OF INTERFERON IN THE CULTURE MEDIUM OF MOUSE K/BALB CELLS: DETECTION BY THE INDUCTION OF 2-5A-SYNTHETASE IN L-929 CELLS.

Hovanessian AG, Robert N
Unite d'Oncologie Virale, Institut Pasteur, 75724 Paris Cedex 15, France
Ann Virol; 132(2):189-194 1981

Capacity of the culture medium of K/Balb cells to induce pppA(2'p5'A)n synthetase (2-5A synthetase) in L-929 mouse cells which contain low levels of 2-5A synthetase without treatment with interferon (IFN), was measured. The level of 2-5A synthetase in L-929 cells after 24-hr treatment was 1286 picomole/mg/hr, a level which was routinely induced by 10-20 effective units of IFN. Culture medium from NIH/3T3 with very low 2-5A synthetase levels did not modify the level in control L-929 cells. Induction of 2-5A synthetase by culture medium indicated that K/Balb cells produce low amounts of IFN which is probably responsible for the presence of the enzyme in such cells. The inducer of 2-5A synthetase was not extractable by phenol. Heating the K/Balb medium at 75 C for 45 min resulted in the loss of the enzyme inducing activity, which is in accordance with the loss of both antiviral and 2-5A synthetase-inducing activities of IFN when heated at the same temperature. The action of the 2-5A synthetase inducer was blocked in the presence of beta-IFN, and by actinomycin D and cycloheximide when added at the start of treatment. Addition of these inhibitors 3 hr after the start of treatment resulted in the inhibition only in the case of cycloheximide. Results indicated that both transcriptional and translational processes were required for the induction of 2-5A synthetase in mouse L-929 cells by culture medium of K/Balb cells, and that the inducer was species specific. This assay may provide a useful, reproducible, and sensitive assay for the detection of trace amounts of IFN. (14 Refs)

OTHER RELATED STUDIES

58. METHYL MERCURY INHIBITS LECTIN-MEDIATED CELL AGGLUTINATION.

Nakada S, Nomoto A, Onozaki K, Imura N
Sch. Pharmaceutical Sciences, Kitasato Univ., 9-1, Shirokane 5-chome, Minato-ku, Tokyo 108, Japan
Ecotoxicol Environ Saf; 5(4):437-442 1981

Effects of methyl mercury (MeM) and inorganic mercury on agglutination of Yoshida ascites sarcoma (YS) cells caused by Ricinus communis agglutination (RC PHA) were studied. Cells were incubated with either compound in medium containing 200 ug RB PHA at 25 C. Samples were stirred vigorously at various time intervals and the cells observed microscopically. In another experiment, YS cells were pretreated with mercurials at 25 C for 30 min, washed 3x with cold phosphate-buffered saline, and RC PHA-mediated agglutination monitored. MeM inhibited RC PHA-mediated agglutination of YS cells above 10(-6) M by incubating at 25 C within 30 min. Extension of incubation to 60 min markedly diminished the inhibitory effect. Inorganic mercury did not inhibit agglutination below 10(-5) M. In the presence of D-galactose RC PHA-mediated YS cell agglutination was completely inhibited. YS cells pretreated with 10(-6) M MeM at 25 C for 30 min could not be agglutinated in the presence of RC PHA to the same extent as untreated cells. More than 90% of pretreated YS cells were not stained with trypan blue. Thus, MeM has a specific adverse effect on function of the plasma membrane of YS cells under these conditions. (6 Refs)

59. PROLACTIN-DEFICIENT VARIANTS OF GH3 RAT PITUITARY TUMOR CELLS: LINKED EXPRESSION OF PROLACTIN AND ANOTHER HORMONALLY RESPONSIVE PROTEIN IN GH3 CELLS.

Ivarie RD, Morris JA, Martial JA
Dept. Molecular and Population Genetics, Univ. Georgia, Athens, GA, 30602
Mol Cell Biol; 2(2):179-189 1982

Expression of prolactin (PL) and the hormonally responsive protein p21 was studied in variants of GH3 rat pituitary tumor cells. GH3 cells in vitro produced approx equal amounts of PL and growth hormone (GH). After exposure to ethylmethanesulfonate (EMS: 300 ug/ml) for 24 hr, survival of GH3 cells was 20-30%. Cultures of 3 of 12 surviving mutants (LP), produced PL in greatly reduced amounts (1.0-2.5% of the amount produced by wild-type GH3 cells). GH production by LP cells varied only approx twofold from GH production by wild-type cells. Radiolabeling experiments showed that reduced secretion of PL resulted from reduced synthesis of PL. Reduced synthesis of PL was repressible by dexamethasone. Reduction in PL synthesis was accompanied by a reduction in p21, which, like PL, is repressible by glucocorticoids (GC). Production of other GC-repressible proteins was not reduced in LP cells. PL production varied in different LP. In the B2 variant reversion to normal PL production occurred at a rate of approx 20%. In the B3 variant reversions occurred at a frequency of 0.5%. Reversion to normal PL production was accompanied by a return to normal amounts of p21, indicating that PL and p21 are closely linked. GH production was phenotypically stable in LP and in GH3 cells not exposed to EMS. Results suggest that EMS, an alkylating agent, promoted an epigenetic change in gene expression. (37 Refs)

60. THE EFFECT OF DOSE RATE AND ADRIAMYCIN ON THE TOLERANCE OF THORACIC RADIATION IN MICE.

Sherman DM, Carabell SC, Belli JA, Hellman S
(c/o Hellman) Dept. Radiation Therapy, Joint Center for Radiation Therapy, 50 Binney St., Boston, MA, 02115
Int J Radiat Oncol Biol Phys; 8(1):45-51 1982

The effect of pre-administration of adriamycin (ADR: 8 mg/kg iv) on radiation tolerance of the lung and esophagus was studied in male C3H-HeJ mice. For the three radiation dose rates of 5, 15, and 70 rad/min, the LD50 curves for oral-esophageal mortality calculated from deaths occurring in the first 30 days (LD50/30) were 2,723, 1,880, and 1,900, respectively. Pulmonary death LD50/160-30 values were 2,574 and 1,636 rad for 5 and 70 rad/min. The dose of radiation necessary to give pulmonary and gastrointestinal toxicity was markedly reduced when ADR was administered 24 hr before irradiation. With a 1-wk interval between ADR administration and irradiation, only the high-dose (1,600 rad) group showed an increased effect. The effect of ADR on the dose rate effect was analyzed. For the same dose of radiation, higher mortality was observed for the higher dose rate (70 rad/min) than with the lower dose rate (5 rad/min). For pulmonary toxicity, a similar difference was observed. The trend for both oral-esophageal and pulmonary mortality indicated that ADR reduces the importance of the dose rate of radiation. Enhancement ratios were calculated. (23 Refs)

61. ANTITUMOR ACTIVITY OF ACYLATED ORIDONIN.

Fujita E, Nagao Y, Kohno T, Matsuda M, Ozaki M
Inst. for Chemical Res., Kyoto Univ., Uji, Kyoto-fu, 611, Japan
Chem Pharm Bull (Tokyo); 29(11):3208-3213 1981

New results on the synthesis of derivatives of the Rabdosia diterpenoid oridonin are presented, with physical, chemical, and spectral data on 14 such compounds. The derivatives were compared with oridonin in tests against Ehrlich ascites carcinoma in mice at doses of 2.5, 5.0, and 10.0 mg/kg. In the series of 14-O-acyl derivatives, activity increased with increase in the acyl carbon chain length. 14-O-Dodecanoyl, tetradecanoyl, and hexadecanoyl derivatives had stronger activity than oridonin although the latter two derivatives were somewhat toxic. The benzoyl derivative had about the same activity as oridonin, whereas the cinnamoyl derivative had no activity. Three 6-O-acyl derivatives had no activity, confirming an earlier hypothesis that hydrogen bonding is a factor in enhancing the antitumor activity or oridonin derivatives. Activity seems to increase with lipophilicity of the oridonin derivatives, suggesting that the ester side chain in 14-O-acyl derivatives plays a carrier role in process(es) related to penetration into cells. (8 Refs)

62. HETEROGENEOUS CHEMOSENSITIVITIES OF SUBPOPULATIONS OF HUMAN GLIOMA CELLS IN CULTURE.

Yung WK, Shapiro JR, Shapiro WR
(c/o Shapiro), Cornell Univ. Medical Coll., 1275 York Ave., New York, NY, 10021
Cancer Res; 42(3):992-998 1982

Six karyotypically distinct clonal cell lines isolated from each of two freshly resected human malignant gliomas were examined for heterogeneity of morphology, in vitro growth rate, and chemosensitivity to 1,3-bis(2-chloroethyl) 1-nitrosourea and cis-diamminedichloroplatinum (II). Each clone was identified karyotypically as having come from the parent tumor. The karyotypic deviations were primarily numerical; chromosome numbers ranged from hypodiploid to near-tetraploid. Three morphological types were recognized: astrocyte-like; squamous-like; and fibroblast-like. The growth rates differed among the clones; the doubling times ranged from 48 to 84 hr in those from one tumor and from 72 to 252 hr in the other. Chemosensitivity was measured by cytotoxicity and/or colony-forming assay. In both assays and in both tumors, heterogeneity of chemosensitivity response to both drugs was demonstrated among the different clones from the same tumor. Dose-response curves from some clones differed statistically (log-probit analysis) from those of others, and when the curves were parallel, their 50% effective doses often differed. For the cytotoxicity assay, the 50% effective doses for BCNU ranged from 43 to 94 ug/ml and for cis-diamminedichloroplatinum (II), from 29 to 340 ug/ml. For the colony-forming assay, the 50% effective doses for 1,3-bis(2-chloroethyl)-1-nitrosourea ranged from 4.5 go 7.0 ug/ml and for cis-diamminedichloroplatinum (II), from 0.35 to 1.40 ug/ml. No correlation was evident between the chromosome number, morphology, growth rates, or chemosensitivities of the clones. These results identified heterogeneity of chemosensitivity among cellular subpopulations in human malignant gliomas. (Author abstract) (20 Refs)

63. IRON(II)-BLEOMYCIN. BIOCHEMICAL AND SPECTRAL PROPERTIES IN THE PRESENCE OF RADICAL SCAVENGERS.

Rodriguez LO, Hecht SM
Dept. Chemistry, Univ. Virginia, Charlottesville, VA, 22901
Biochem Biophys Res Commun; 104(4):1470-1476 1982

The effect of hydroxyl free and dioxygen free radical scavengers on the ability of Fe(II)-bleomycin (Fe(II)-BLM) to degrade radiolabeled PM-2 DNA was studied by the release of (3H)thymine. Dimethylsulfoxide (DMSO) completely suppressed the degradation of DNA by Fenton's reagent and H2O2. The damage mediated by bleomycin A2 in the presence of Fe(II) was not affected by the same amount of DMSO. The release of (3H)thymine from radiolabeled PM-2 DNA by 2.5 uM bleomycin was the same in the presence or absence of 80 milliM t-butyl phenylnitrone (BPN). As anticipated, DNA degradation by Fenton's reagent was completely suppressed by this BPN treatment. The scavenger tetrakis(4-N-methylpyridyl)porphineiron(III) was without effect as an inhibitor of DNA degradation. Corroborative evidence was also obtained by study of the intensity of the epr (electron paramagnetic resonance) signal produced by Fe(II)-BLM in the presence of BPN, compared to that produced by an equimolar amount of Fe(II) and excess H2O2. It is concluded that the fragmentation of DNA produced by Fe(II)-BLM is not due to either hydroxyl free or dioxygen free radicals. It is suggested that DNA degradation is initiated by an 'active complex' consisting of BLM, metal and oxygen that functions by abstracting free H from susceptible sites on DNA. (31 Refs)

64. INDUCTION OF CHROMATID BREAKAGE BY CLASTOGENS IN CELLS OF G2 PHASE.

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Dept. Cell Biology, Univ. Texas M. D. Anderson Hosp. and Tumor Inst. at Houston, Houston, TX, 77030
Mutat Res; 93(1):185-193 1982

Clastogenicity of several compounds was tested in cultures of human peripheral blood cells in G2 phase. Cells were exposed simultaneously to Colcemid and actinomycin D (AMD: 2.8 uM for 15, 30, 45, or 60 min or 2.8, 1.4 or 0.28 µM for 60 min). Chromosome breakage was induced in a dose-dependent manner. The most frequent aberrations were chromatid breaks; chromatid exchanges were rare. In a modified procedure, cells were exposed to 2.8 uM AMD for 90 min, but to Colcemid for only the last 60 min. Among 100 metaphase figures 95% had chromatid breaks; the av number of breaks/cell was 3.77. Autoradiographic studies indicated that all chromatid aberrations occurred during G2 phase. Additional clastogens were tested at 100 uM concentrations (or at lower concentrations when 100 uM was too toxic). Chromatid breaks were produced by adriamycin, bleomycin, neutral red, gentian violet, and 1,4-dihydroxy-5,8- [*2-(2 hydroxymethyl)amino*]*ethylamino* -9,10-anthracenedione at 15-100x the frequency produced in controls. No increases in the frequency of chromatid breaks were produced by mitomycin C, hydroxyurea, ethidium bromide, or cytosine arabinoside. Cis-platinum II produced borderline results. N-Methyl-N'-nitrosoguanidine was mildly clastogenic in G2 phase. Results indicate that a simple protocol can be used to determine clastogenicity in G2-phase cells. (8 Refs)

65. TOXICITY, INTERSTRAND CROSS-LINKS AND DNA FRAGMENTATION INDUCED BY ACTIVATED' CYCLOPHOSPHAMIDE IN YEAST: COMPARATIVE STUDIES ON 4-HYDROXYPEROXY-CYCLOPHOSPHAMIDE, ITS MONOFUNCTIONAL ANALOGUE, ACROLEIN, PHOSPHORAMIDE MUSTARD, AND NOR-NITROGEN MUSTARD.

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(c/o Brendel) Institut fur Mikrobiologie, Universitat Frankfurt, Theodor-Stern-Kai 7, Haus 75, 6000 Frankfurt/M, W. Germany
Chem Biol Interact; 39(1):1-15 1982

Activated cyclophosphamide (CP) is known to achieve its cytotoxic and alkylating capacity upon spontaneous hydrolytic breakdown of the oxazaphosphorine ring structure. Treatment of yeast cells with the chemically activated form of CP (4-hydroperoxy-CP, 4-OOH-CP) and with several potentially toxic cleavage products revealed that cytotoxicity is closely linked to the formation of DNA interstrand cross-links and to DNA fragmentation. While this holds true for 4-OOH-CP and its bifunctional alkylating breakdown products, phosphoramide mustard (PM) and nor-nitrogen mustard (NNM), equimolar concentrations of acrolein and the monofunctional analogue of activated CP were inactive. NNM, the ultimate cleavage product within the successive degradation of the oxazaphosphorine structure was 5x more toxic than 4-OOH-CP, whereas the cytotoxic action of PM was only slightly enhanced. The high cytotoxicity of NNM was matched by its ability to induce DNA interstrand cross-links: at concentrations and treatment times producing equal cell killing, 4-OOH-CP and NNM produced the same extent of cross-linking and DNA fragmentation. Biochemical potency of NNM is in contrast to data found with the NBP colorimetric assay which suggest that NNM loses its alkylating activity at neutral pH. 4-OOH-CP and PM are much more stable than predicted from half-life measurements performed via the NBP colorimetric assay: they retain a considerable fraction of their cytotoxic and cross-linking activity in spite of a 12-hr preincubation at pH 7 and 36 C. (Author abstract) (24 Refs)

66. NUCLEAR CATALYZED ANTIBIOTIC FREE RADICAL FORMATION.

Bachur NR, Gee MV, Friedman RD
Lab. Clinical Biochemistry, Baltimore Cancer Res. Program, NCI, Baltimore, MD, 21201
Cancer Res; 42(3):1079-1081 1982

Nuclei isolated from rat liver, heart, and kidney catalyze oxygen consumption in the presence of reduced pyridine nucleotide (NADPH) and quinone or quinone-imine antibiotics such as Adriamycin, daunorubicin, actinomycin D, mitomycin C, and streptonigrin. The Km and Vmax values for NADPH were 2.4 x 10(-3) M and 3 x 10(-8) mol O2 per min per mg protein and Km values for the antibiotics ranged from 1.4 x 10(-4) M to 5.9 x 10(-6) M. Metabolism of the anthracycline antibiotics, ie, reductive glycosidase reaction, occurs in reaction mixtures after all oxygen is consumed. During the reaction, free-radical species of Adriamycin and daunorubicin are detectable by electron paramagnetic resonance spectrometry. These observations indicate that some cytotoxic antibiotics can be activated to a free-radical state at the site where damage to nuclear DNA may result. (Author abstract) (23 Refs)

67. EFFECT OF SCHEDULING OF COMBINATIONS OF 5-(3,3-DIMETHYL-1-TRIAZENO)-IMIDAZOLE-4-CARBOXAMIDE AND 1-(2-CHLOROETHYL)-3-(4-METHYLCYCLOHEXYL)-1-NITROSOUREA ON THE HARDING-PASSEY AND CLOUDMAN S91 MOUSE MELANOMAS.

Hill HZ, Hill GJ
Dept. Radiology, Section Cancer Biology, Coll. Medicine and Dentistry New Jersey-New Jersey Medical Sch., Neward, NJ, 07103
Cancer Res; 42(3):838-842 1982

Harding-Passey mouse melanoma (HP) cells (10(6)) were administered ip to female BALB/c x DBA/2F1 (hereafter called CD2F1) mice on Day 0. We showed earlier that a single dose of 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC) administered on Day 0 or on subsequent days was equally effective regardless of the day of administration. We now show that a single dose of 10 mg of 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (MeCCNU) per kg was most effective in prolonging survival of HP-bearing CD2F1 mice when administered on Day 0. There was then a decline in effectiveness to Day 10, at which time the increase in survival of the drug-treated animals was no longer significant. The effect of sequential scheduling of DTIC and MeCCNU on HP was studied. The first drug was given on Day 0 or on Day 10. The second drug followed on the same day or on subsequent days. The greatest enhancement of survival was seen when DTIC was administered on Day 0 and MeCCNU on Day 1. Nine of 10 mice on this schedule were cured. When treatment of HP was started on Day 10, the most enhancement was again seen for DTIC on Day 10 and MeCCNU on the next day. Reversal of the order of the two drugs produced less prolongation of survival and fewer cures. The effect of scheduling two doses of DTIC was also studied using the HP model. The first dose was given on Day 0 or on Day 10. The second dose produced the greatest enhancement of survival when administered 3 to 4 days after the first dose, but the enhancement was less than that seen when DTIC was followed by MeCCNU. For comparison, the two drugs were also studied in female DBA/2 mice carrying the Cloudman S91 melanoma. In combination, on Day 0, in only one of three experiments was survival prolonged beyond the controls. Other schedules were ineffective. The enhancement seen when HP-bearing CD2F1 mice are treated with the best combination of the two drugs is clearly not seen with S91. The results imply that dosage scheduling in the treatment of murine melanomas must be individualized. Extrapolation to the human situation suggests the same conclusion. (Author abstract) (14 Refs)

68. EFFECTS OF SYSTEMIC HYPERTHERMIA AND INTRAHEPATIC INFUSION WITH 5-FLUOROURACIL.

Daly JM, Smith G, Frazier OH, Dudrick SJ, Copeland EM
Dept. Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

Cancer; 49(6):1112-1115 1982

Potential hepatotoxicity from systemic hyperthermia (43 C) - simultaneous hepatic artery infusion with 5-FU was evaluated in an animal model. Twenty-two dogs had aorta-vena caval shunts (8 mm Dacron grafts) placed, and 10 of these dogs had silastic catheters inserted in their hepatic arteries. Two wk later, Group I (n = 8) was heated to 43 C for 1 hr (distal esophageal intrahepatic temperature) using the shunts and blood-heat exchangers; Group II (n = 6) was heated to 43 C for 1 hr with simultaneous intrahepatic infusion of 5-FU (10 mg/kg); Group III (n = 8) was shamheated (37 C) and underwent a 1 hr intrahepatic infusion with 5-FU (10 mg/kg). Serum alkaline phosphatase, SGOT, SPGT (IU/ml) and bilirubin were measured, and liver biopsies were obtained at 0 and 1 hr, at 1 and 7 days. Mean SGOT levels increased significantly (p less than 0.05) in Group II from 19 -2 to 31 -6 and 63 -18 at 1 hr and 1 day; these levels rose slightly in Group I from 31 -5 to 40 -8 and 47 -8 at 1 hr and 1 day. Hepatocellular enzyme levels returned to normal at 7 days in both groups. Mean SGOT and SGPT levels remained similar in Group III at all time periods. No significant differences in mean serum alkaline phosphatase or bilirubin levels were noted. There was no histologic evidence of hepatocellular necrosis at any time period. Survival was 6/8, 5/6 and 8/8 dogs in Groups I, II, and III, respectively. Systemic hyperthermia to 43 C for 1 hr in dogs does not adversely affect serum hepatic enzymes or cell structure; reversible serum hepatic enzyme changes occurred when hyperthermia was combined with hepatic artery infusion with 5-FU. (Author abstract) (18 Refs)

69. PROSTATIC CANCER.

Loprinzi CL
Maricopa County General Hosp., 2601 E Roosevelt St., Phoenix, AZ, 85008

South Med J; 75(2):193-196 1982

Prostatic cancer is a common cause of morbidity and mortality in the United States. Although many new serologic and radiologic procedures are now used in its diagnosis, the rectal examination still remains the best diagnostic test. Staging is essential for effective treatment. Treatment of prostatic cancer varies, with observation in Stage A1; surgery and/or irradiation for stages A2, B, and C; and hormonal or cytotoxic drugs for symptomatic Stage D. (Author abstract) (38 Refs)

70. DELIVERY OF CHEMOTHERAPEUTIC AGENTS TO THE CENTRAL NERVOUS SYSTEM.

Cohen JI
Duke Univ. Medical Center, Durham, NC, 27710

Med Hypotheses; 8(1):103-104 1982

Tetanus toxin is proposed as a vehicle for delivery of chemotherapeutic agents across the blood-brain barrier for treatment of infections, malignant tumors, or inborn metabolic malfunctions. Because use of the unmodified toxin would be dangerous, modification by freezing or papain digestion might be employed to reduce toxicity. Coupling of therapeutic agents to the toxin presents theoretical rather than practical problems. The proposal suggests an alternative to disrupting the blood-brain barrier. (7 Refs)

71. EFFECT OF COMBINED AND SEPARATE ADMINISTRATION OF EXOGENOUS VITAMINS ON THE INCIDENCE OF CHROMOSOME ABERRATIONS IN RATS SUBJECTED TO SUBACUTE EXPOSURE TO SODIUM FLUORIDE.

Akhundov VIu, Aliev AA, Kul'gavin AE, Sarina TN
Inst. Botany, Baku, USSR
Izv Akad Nauk Azerb [Biol]; (4):3-5 1981

Potential antimutagenic activity of vitamins E, A, and C was studied in random-bred albino rats subjected to po administration of sodium fluoride (SF) at 0.1 LD50 (0.32 mg/100 g). SF increased the incidence of chromosome aberrations in the bone marrow. Daily, po administration of vitamin E alone or in combination with vitamins A and C reduced the mutagenic effect of SF. (2 Refs) (In RUS)

72. AN ANTAGONISTIC EFFECT BETWEEN AZIRIDINE AND DIAZIRIDINE ON THEIR CYTOTOXIC ACTIVITIES AGAINST L-1210 MOUSE LEUKEMIA CELLS.

Takase S, Watanabe M, Shiratori O, Hata Y
(c/o Hata) Shionogi Res. Lab., Shionogi and Co., Ltd., Fukushima-ku, Osaka 553, Japan
Biochem Biophys Res Commun; 104(2):746-749 1981

The effects of combining 1-methyl-2-p-chlorophenylaziridine (AZ) and 1,2-dimethyl-3-p-chlorophenyldiaziridine (DAZ) on cytotoxicity toward L-1210 mouse leukemia cells was examined. Both compounds caused clear concentration-dependent inhibition of cell growth when tested separately. When combined, the inhibition ranged from 45% with 100% AZ (5.946 ug/ml), to approx 36% with equal proportions of AZ and DAZ, to over 48% with DAZ alone (168.2 ug/ml). All combinations of the two compounds had lower percentage inhibitions than the separate compounds, indicating a clear antagonism. The result is in agreement with similar behavior of a rat liver microsomal system investigated earlier, in which competition for cytochrome P-450 active center was considered responsible for the reduction of cytotoxicity with combined agents. (4 Refs)

73. SPECIFICITY OF TRANSPORT OF BLEOMYCIN AND COBALT-BLEOMYCIN IN L5178Y CELLS.

Uehara Y, Hori M, Umezawa H
Inst. Microbial Chemistry, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141, Japan
Biochem Biophys Res Commun; 104(2):416-421 1981

Tritium labeled peplomycin (PEP) was used to investigate the transport mechanism of bleomycin in L5178Y mouse leukemic cells. Co enhanced the initial rate of PEP uptake, but Cu, Zn, Fe(II), and Fe(III) had no effect. Initial velocities of uptake of Pep-Co chelate were similar at 0 and 37 C. Kinetic analysis of initial uptake of PEP-Co over a concentration range of 0.43-67 uM appeared to be biphasic. A 70-fold excess of PEP-Co 2 isomers of bleomycin A2-Co, or bleomycinic acid inhibited transport of 0.4 uM (3H)PEP-Co, but the same concentration of PEP, PEP-Cu chelate, bleomycinic acid, or Co ion did not. The Pep-Co transport system described here may be a model for bleomycin group antibiotics which could aid in the study of differences in uptake and efficacy among different tumor types. (16 Refs)

74. DRUG ANTIMUTAGENESIS (REVIEW).

Zolotareva GN, Akaeva EA
Res. Inst. Biological Testing of Chemical Compounds, Moscow Oblast', USSR
Khim Farm Zh; 15(12):9-14 1981

The results of screening for chemical compounds that reduce the mutagenic properties of drugs but do not affect their therapeutic activity are reviewed. The group of compounds that reduce the level of chemical mutagenesis includes nucleic acids and their metabolites, natural metabolites (spermine, ATP, thiouracil, gibberellic acid), inhibitors of free radical reactions, acridine orange, dimethylsulfoxide, streptomycin, chloramphenicol, actinomycin D, hexamidine, and vitamins A, E. and C. It was emphasized that testing of the potential antimutagenic activity should be carried out in a number of test-systems and in a wide range of concentrations. (92 Refs) (In RUS)

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ANTITUMOR AGENT EFFICACY IN VIVO

1. EFFECT OF CIS- AND TRANS-DICHLORODIAMMINEPLATINUM(II) ON HUMAN TUMOR CELL PROLIFERATION IN DIFFUSION CHAMBERS IN VIVO.

Ambrose KR, Lowrey JS
Health and Safety Res. Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Cancer Res; 42(5):1769-1773 1982

The cis and trans isomers of dichlorodiammineplatinum(II) (DDP) were tested for their ability to inhibit human tumor cell proliferation in vivo. Cell-impermeable diffusion chambers containing KB target cells were surgically implanted in the peritoneal cavities of Fischer rats, which were, 1 day later, given ip injections of cis-DDP (0.25 to 8.0 mg/kg), trans-DDP (8.0 mg/kg), or 0.9% NaCl solution. Radiolabeled cis- and trans-[195mPt]DDPs were used to monitor the diffusion of DDP within the chamber fluid and the binding or uptake of DDP by the target cells. Cell counts following injection showed that cis-DDP induced a progressive, dose-dependent loss in cell number so that, by the 2nd day, the chambers of animals re-

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ceiving cis-DDP (8 mg/kg) contained less than 10% of the cell number found in the control or trans-DDP-treated chambers. Despite the relative lack of biological activity of the trans-isomer, between two- and three-fold greater levels of 195mPt activity were detected in the fluid and target cells in chambers of animals receiving trans-[195mPt]DDP compared to cis-[195mPt]-DDP injected animals. Scanning electron micrographs of target cells from cis-DDP treated rats showed certain morphological features (cell surface blebs and the appearance of giant cells) that were not found in control target cell populations. The diffusion chamber system was shown to be a reproducible, sensitive assay system which differentiated between cis-DDP, a potent antitumor drug, and trans-DDP, a biologically ineffective isomer. In addition, it was possible using 195mPt-labeled DDP in this assay system to quantitate the relative concentrations of the two isomers both surrounding and within the target cells. (Author abstract) (28 Refs)

2. ANTITUMOR ACTIVITY OF THE 3'-CHLOROETHYLNITROSOUREA ANALOG OF THYMIDINE AND THE PREVENTION BY COADMINISTERED THYMIDINE OF LETHALITY BUT NOT OF ANTICANCER ACTIVITY.

Lin TS, Fischer PH, Marsh JC, Prusoff WH
Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Cancer Res; 42(5):1624-1629 1982

The effect of the 3'-nitrosourea analog of thymidine (3'-[3-(2-chloroethyl)-3-nitrosoureido]-3' deoxythymidine; 3'-CTNU) on the growth of the murine L1210 and P388 leukemias in mice was investigated. A single injection of 3'-CTNU (40 mg/kg) was minimally toxic to mice bearing the L1210 leukemia and produced 60-day survivors. The coadministration of thymidine did not prevent the initial loss of wt caused by 3'-CTNU but did prevent the lethality otherwise produced in non-tumor-bearing mice. A single dose of thymidine (2 g/kg) administered to L1210-bearing mice had no anticancer activity and when coadministered with 3'-CTNU had no detrimental effect on the potent antitumor effects of 3'-CTNU. Similar results were obtained against P388 leukemia. The hematopoietic toxicity produced by the administration of 3'-CTNU to non-tumor-bearing mice, as evidenced by changes in the white blood cells, neutrophil, and agar diffusion chamber precursor cell concentrations in the hematocrit and in bone marrow cellularity, could not be prevented by thymidine. Therefore, the lethality produced by 3'-CTNU is probably not related to hematopoietic toxicity since the coadministration of thymidine completely prevented any lethality. (Author abstract) (40 Refs)

3. EFFECT OF DIATOMITE PARTICLES ON THE DEVELOPMENT OF A SYNGENEIC LEUKEMIA IN MICE.

Bustuoabad OD, Genovese JA, Pasqualini CD
Departamento de Leucemia Experimental, Instituto de Investigaciones, Hematologicas Academia Nacional de Medicina, Buenos Aires, Argentina
Medicina (B Aires); 41(Suppl):215-220 1981

Diatomite particles (DP) have toxic effect on macrophages. Effect of dosage and size of DP on macrophage was investigated. DP consisted of 54.3% of SiO2, 25.1% of CaO, 3.6% Al2O3, etc; the size was between 5-12 microns and two suspensions in physiologic solution were prepared containing 0.0002 mg and 1 mg DP/ml. Male BALB/c mice 2 mo old wt 20-25 g were inoculated sc with spontaneous lymphatic leukemia and ip with 1 ml of DP suspension simultaneously or DP suspension was administered 14 days earlier. Each group of animals consisted of 40 animals or more. All animals in control group developed tumors on day 12 and all the other groups by day 19. Nineteen days later the size of tumors in the control group was 224 cubic mm (mm3); 53 mm3 and 99 mm3 in Group 1 which received DP 14 days earlier, and 69 mm3 and 138 mm3 in Group 2 which received DP simultaneously. All the animals in the control group were dead 22 days after inoculation with spontaneous lymphatic leukemia; 12/42 and 7/40 survived in Group 1 and 10/44 and 4/48 survived in Group 2. It was concluded that resistance obtained with DP on tumor development is associated with nonspecific stimulation of the macrophages. (13 Refs) (In SPA)

4. A COMPARISON OF THE EFFICACY FOR ANTITUMOR ACTIVITY OF THE NON-STEROIDAL ANTIESTROGENS ANALOG II AND TAMOXIFEN IN 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED RAT MAMMARY TUMORS.

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Cancer Lett; 15(3):261-269 1982

The efficacies of analog II (AII), a cyclopropyl derivative of stilbene, and of tamoxifen (TX) in producing the regression of established 7,12 dimethylbenz[a]anthracene (DMBA)-induced rat mammary tumors and preventing the formation of new tumors as palpable masses were compared. Female Sprague-Dawley rats were used. No overt harmful or toxic effects were noted in any of the groups as a result of treatment with either TX or AII, nor could any evidence for such be determined by histological examination following complete necropsy and tissue sampling at the end of the 7-wk treatment period (TP). Both antiestrogens effectively decreased the percentage of animals with increased tumor vol and increased the percentage of animals with decreased tumor vol. AII significantly altered tumor growth (TG) between the third and fifth wk of TP and TX produced similar alterations in TG between the fifth and seventh wk. At the end of the TP, four of the eight AII-treated animals developed 9 new tumors while six of the seven control animals developed 12 new tumors and seven of the eight TX-treated animals developed 17 new tumors. Thus, AII protected 50% of the animals against new tumor development while only 12% of the TX-treated animals and 14% of the controls were similarily protected. Results indicate that AII is more effective than TX in protecting animals against development of new tumor masses during TP. (17 Refs)

5. EFFECTS OF ESTROGENS AND ANTIESTROGENS ON ANDROGEN-DEPENDENT GROWTH OF SHIONOGI CARCINOMA 115: ROLE OF ESTROGEN RECEPTOR.

Nohno T, Omukai Y, Watanabe S, Saito T, Senoo T
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Cancer Lett; 15(3):237-244 1982

The effects of estrogens and antiestrogens on Shionogi carcinoma 115 (SC115) tumor growth in relation to the receptor binding of androgen or estrogen were examined. Male DS mice (6-18 wk old) were used. Castration was performed 3 days prior to drug treatment. The growth of SC115 was dependent on androgens. Cumulative lethal takes were evaluated on day 60, and were 352 of 367 (96%) in males and 13 of 102 (13%) in females. When estradiol (ES) or diethylstilbestrol (DES) was given to intact male mice at a daily dose of 2 mg/

kg, TG as well as the wt gains of seminal vesicles (SV) and prostate glands was inhibited. TG was stimulated with 5 mg/kg nitromifene. Consistent decrease in tumor wt was observed in intact animals after administration of 0.5-50 mg/kg tamoxifen (TX). In the castrated mice (CM) given 4 mg/kg of testosterone propionate from day 0, 5 mg/kg of TX had no effect on TG but 20 mg/kg TX slightly increased the tumor wt. The wt of SV decreased at the higher dose of TX. Androgen receptors (AR) in the tumor cytosol of androgen-treated CM were 32.5 +-5.5, 28.9 +-6.3, and 39.3 +-8.2 femtomole/mg protein at TX doses of 0, 5, and 20 mg/kg, respectively. No remarkable change in histology of SC115 was observed when estrogens and antiestrogens affected the TG. ES competed effectively for [3H]dihydrotestosterone (DHTT) binding but DES and TX did not. DES in 100-fold molar excess did not maximally inhibit [3H]ES binding to SC115 cytosol and low concentrations of DHTT effectively decreased a fraction of [3H]ES binding. Results indicated that ES most likely binds not only to ER but also to AR in the tumor cytosol. (17 Refs)

6. ANTITUMOR EFFECT OF DICYCLOHEXYLAMMONIUM SULFATE, A POTENT INHIBITOR OF SPERMIDINE SYNTHASE AGAINST P388 LEUKEMIA.

Ito H, Hibasami H, Shimura K, Nagai J, Hidaka H
Dept. Pharmacology, Mie Univ. Sch. Medicine, Tsu, Mie 514, Japan
Cancer Lett; 15(3):229-235 1982

The effect of dicyclohexylammonium sulfate (DCHA) on P388 mouse leukemia was investigated; correlation between the antitumor effect and the spermidine concentration in ascites tumor cells and spleen is discussed. Female mice of BDF1 hybrid strain were used. DCHA administered daily for 6 days starting 24 hr after tumor inoculation prolonged the survival time of mice bearing the tumor. The percentage of mean survival days of treated relative to control mice were 110.3, 133.3, 187.2, 138.5, and 118.0 at DCHA dosages of 10, 25, 50, 75, and 100 mg/kg, respectively. A dose of 50 mg/kg/day was the most effective. DCHA was non-toxic at the dose of 100 mg/kg administered daily for 6 days. The treatment of non-leukemic mice with DCHA, 50 mg/kg ip daily for 6 days, had no significant effect on av spleen wt, compared with 0.15 M NaCl treatment. Spleen wt increased by approx 30% at 7 days after the tumor inoculation. DCHA treatment did not prevent the tumor-induced increase in splenic wt. A dose of 50 mg/kg DCHA ip administered daily for 6 days caused a diminution of the increase in concentration of spermidine, with little effect on the spermidine concentration in the ascites tumor cells and spleens of mice bearing the tumor. The depletion of spermidine in the ascites tumor cells might be a cause of the suppression of tumor growth. (26 Refs)

7. EFFECT OF MEDROXYPROGESTERONE ACETATE ON DMBA-INDUCED RAT MAMMARY CARCINOMA AND ON IMMUNOLOGICAL REACTIVITY.

Spreafico F, Filippeschi S, Malfiore C, Noseda S, Falautano P, Serraglia N
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Eur J Cancer Clin Oncol; 18(1):45-51 1982

The antineoplastic activity of medroxyprogesterone acetate (MPA) was investigated in rats bearing DMBA-induced mammary carcinomas, a classical model of hormone-dependent tumor. Using a repeated injection schedule of relatively short duration, MPA was markedly effective (80% CR + PR) not only on relatively small (1-1.5 cm) tumors but also on advanced (4.5-5.5 cm) neoplasms. MPA effectiveness was comparable to that of a frankly toxic adriamycin regimen. In antitumorally effective schedules MPA was incapable of significantly affecting in either direction cellular and humoral immunological reactivities in rodents. (Author abstract) (23 Refs)

8. EFFECT OF X-RAYS AND CYCLOPHOSPHAMIDE ON SOLID TUMORS AND NATURALLY OCCURRING METASTASES IN MICE.

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Cancer Res; 42(5):1943-1949 1982

Combinations of single doses of x-rays given locally to a transplanted tumor and single ip doses of cyclophosphamide (CY) were tested in mice bearing solid transplanted fibrosarcomas. The end points examined were growth delay and local control of the implanted tumor, the incidence of distant metastases, and survival times free of either local recurrence or metastases. Growth delay and local control increased more steeply with x-ray dose than with dose of CY. From 8 to 10 days of extra regrowth delay required only 10 to 20% extra x-ray dose, but it required a doubling of CY dose from three-eighths to three-fourths of the maximum tolerated dose. The incidence of metastases and the survival time of the mice also depended more upon the local dose of x-rays than that of CY. This result was not expected and suggests that metastases are eliminated more certainly if the primary (implanted) tumor is locally controlled on a long-term basis. A significant proportion of mice, over 50%, was cured of both the transplanted tumor and distant metastases only when the highest doses of both x-rays and CY were given simultaneously. Extended intervals between the two agents gave inferior results, intervals of 8 days giving significantly worse results, but 4 days giving not significantly worse results than simultaneous administration, especially when the x-ray treatment was given first. The interval of 4 days may, however, be sufficient to avoid the enhancement of radiation injury in normal tissues. (Author abstract) (25 Refs)

9. ANTITUMOR ACTIVITY OF BETA-CAROTENE, CANTHAXANTHIN AND PHYTOENE.

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Brigham and Women's Hosp., 180 Longwood Ave., Boston, MA, 02115
Oncology; 39(1):33-37 1982

Mice were given either beta-carotene or either of two carotenoids with no vitamin A activity - canthaxanthin or phytoene - or placebo. Skin tumors were induced in each group by each of three methods: (1) UV-B (290-320 nm); (2) dimethylbenz(a)anthracene (DMBA)/croton oil applications; (3) DMBA followed by low-dose UV-B. For tumors induced by UV-B alone, beta-carotene-phytoene- and canthaxanthin-treated mice developed fewer tumors per mouse, with a delay in tumor appearance, than did control mice. For tumors induced by DMBA/croton oil or DMBA/UV-B, mice receiving beta-carotene showed a significant difference in tumor numbers and appearance time from placebo mice; phytoene and canthaxanthin treatment had no effect. (Author abstract) (16 Refs)

ANTITUMOR AGENT EFFICACY IN VITRO

10. CORRELATES OF VINCRISTINE RESISTANCE IN FOUR MURINE TUMOR CELL LINES.

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Cancer Lett; 15(3):335-341 1982

Four murine leukemia cell lines with different degrees of resistance to vincristine (VCR) were examined, and resistance was correlated with a variety of transport parameters. The cell lines were L1210, P1534, P388, and P388/VCR. The percentage of max increase in life span of experimental animals compared to controls (%ILS) for each VCR dose level from 200 mg/kg to 50 mg/kg is summarized for each tumor line. The rankings of each tumor line by %ILS were similar for doses of 25, 50, and 100 mg/kg. Minimal VCR toxicity was observed at doses of 200 mg/kg. The P1534 tumor line was most sensitive to VCR, with a %ILS of 290 at a dose level of 50 mg/kg. The P388/VCR line was resistant to VCR, with no significant augmentation of survival following VCR treatment at this dose level. The time course of VCR uptake in the four murine cell lines is illustrated for an external VCR concentration of 1 uM. Uptake proceeded rapidly over the initial 10 min and then began to slow. A steady-state value was attained between 40 and 60 min. Initial velocity, recorded over the initial 60 sec of uptake, is summarized for the tumor lines. Efflux velocity was measured and the values obtained by dividing the two velocities were highest for P1534, the line most sensitive to VCR. P388/VCR had the lowest value. Data suggest that cells capable of retaining VCR intracellularly for longer periods of time are more apt to be killed by VCR. (7 Refs)

11. MODULATION OF BLEOMYCIN CYTOTOXICITY.

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Antimicrob Agents Chemother; 21(4):595-600 1982

Lethal effects of a 75-ug/ml concentration (approx 5 x 10(-5) M) of bleomycin on stationary-phase haploid or diploid cells of the eukaryote Saccharomyces cerevisiae were negated in the presence of 0.05 M phosphate buffer (pH 7). High cell densities (2 x 10(8) cells per ml) further inhibited killing. Multiphasic survival curves resulting after treatments in deionized water (pH 6.7) suggested the presence of cells with differing susceptibilities either at the start of treatment periods or as a result of resistance which developed during exposure to antibiotic. To identify a delayed effect, prolonged lethal consequences of the action of bleomycin were investigated under liquid-holding conditions. Survival of untreated early-stationary-phase yeast cells was not significantly affected by incubation without antibiotic for 6 or 36 hr in non-nutrient buffer or water. However, increased killing resulted after bleomycin-treated cells were incubated in the absence of bleomycin or buffer. Moreover, cells which had never been exposed to the antibiotic lost considerable colony-forming ability as a result of incubation with bleomycin-treated cells, indicating the efflux of bleomycin or a reaction product. The findings have implications for both experimental cell studies and cancer therapy, as well as for the chemical mechanisms by which a metal-bleomycin complex could cause killing. (Author abstract) (33 Refs)

12. THE SIGNIFICANCE OF DNA CROSS-LINKING TO CIS-DIAMMINEDICHLOROPLATINUM(II)-INDUCED CYTOTOXICITY IN SENSITIVE AND RESISTANT LINES OF MURINE LEUKEMIA L1210 CELLS.

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Chem Biol Interact; 39(2):169-180 1982

The cross-linking of DNA by cis-diamminedichloroplatinum(II) (cis-DDP) has been studied in a murine leukemia L1210 line (L1210/0) and a 30-fold resistant subline (L1210/DDP2) utilizing the technique of alkaline elution. The kinetics of cross-link formation were similar in both cell lines. After 1-hr treatment with cis-DDP, cross-linking continued to increase to a maximum at 12 hr posttreatment. Although cross-linking decreased by 24 hr some lesions were seen to persist. After 72 hr interstrand cross-links were completely removed by both cell lines; however, 50% of the DNA-protein cross-links still remained in the sensitive cells even though they were undetectable in the resistant subline. To correlate cross-linking with cytotoxicity, a range of drug concentrations were used for concomitant growth inhibition studies and alkaline elution analyses. In addition to the 30-fold resistant sublines, two other sublines developed in our laboratory which show 20-and 50-fold resistance to cis-DDP were included in these determinations. All the resistant sublines exhibited the same degree of cross-linking at the same applied drug doses although these doses elicited markedly different cytotoxicities; cross-linking varied only with applied drug concentrations. The degree of cross-linking in L1210/0 was also directly related to the dose of cis-DDP. However, the sensitive cell line displayed equivalent total cross-linking at a five-fold lower applied dose. This may implicate an uptake phenomenon as a contributor to resistance. However, such a phenomenon can account for only part of the resistance observed as there existed six-fold more total cross-links and nine-fold more interstrand cross-links in L1210/DDP2 at doses that were equitoxic to L1210. This suggests the existence of a more critical cytotoxic lesion that was not detectable by alkaline elution, probably intrastrand cross-links. Resistance could be due to a differential removal of these lesions. (Author abstract) (31 Refs)

13. PURINE NUCLEOSIDE ANALOGUES INHIBIT THE REPAIR OF RADIATION-INDUCED POTENTIALLY LETHAL DAMAGE IN MAMMALIAN CELLS IN CULTURE.

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Dept. Experimental Radiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan

Int J Radiat Biol; 41(3):343-346 1982

Effects of nucleoside analogs, including 3'-deoxyguanosine, 3'-deoxycytidine, 3'-deoxyuridine, 2',3'-dideoxythymidine, and beta-D-arabinofuranosyladenine, on repair of potentially lethal damage (PLD) in irradiated cells were studied in hamster HA-1 cells in the stationary phase. Of the nucleosides tested, only purine analogs inhibited the repair of PLD significantly at relatively low doses. (10 Refs)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

14. HETEROCYCLIC AMPLIFIERS OF PHLEOMYCIN.

Brown DJ, Grigg GW
John Curtin Sch. Medical Res., P. O. Box 334, Canberra City 2601, Australia
Med Res Rev; 2(2):193-210 1982

Fused and unfused heterocyclic amplifiers of phleomycin are reported. Fused amplifiers include purines, heteromonocyclic compounds and their benzo derivatives, purine-like heterobicyclic compounds, and s-triazolopyridines and related systems. Unfused heterobicyclic amplifiers include thiazolylpyridines, pyridinyl- and pyrazolyl-pyrimidines, and bipyrimidines and miscellaneous systems. Antitumor activity of phleomycin plus heterocyclic amplifiers in rat Walker 256 carcinosarcoma, mouse Ehrlich ascites carcinoma, Mouse S180 sarcoma, and Escherichia coli in vitro is tabulated. (54 Refs)

15. SEQUENTIAL COMBINATION OF VINCRISTINE, ADRIAMYCIN AND CYCLOPHOSPHAMIDE (VAC), AND RADIOTHERAPY IN ADVANCED NON-SMALL-CELL LUNG CANCER.

Wils JA, Ribot JG
Dept. Internal Medicine, St. Laurentius Hosp., Mgr. Driessenstraat 6, 6043 CV Roermond, The Netherlands
Neth J Med; 25(2):43-46 1982

Subjects with inoperable stage III or IV lung cancer [5 adenocarcinoma (AC), 6 large-cell anaplastic carcinoma (LCAC), and 15 squamous-cell carcinoma (SCC)] were treated with vincristine (1 mg), adriamycin (50 mg), and cyclophosphamide (1000 mg) iv, followed 2-3 wk later by radiotherapy (4,230 cGy applied in 18 fractions over 4.5 wk). Chemotherapy was repeated every 3-4 wk over a 3.5-yr period. Subjects not progressing after 12 doses of adriamycin were transferred to 5-fluorouracil (500 mg iv) until progression or 2 additional yr had elapsed in complete responders. Complete regression with median survival time (MST, from onset of chemotherapy) of 19 mo (range 3-35+ mo) was achieved in 6 subjects (2 AC, 1 LCAC, and 3 SCC). Partial regression with MST of 11 mo (range 5-18 mo) was achieved in 10 subjects (1 AC, 2 LCAC, and 7 SCC). The remaining 10 subjects with MST of 5 mo (range 3-10 mo) included 6 who were unresponsive and 4 who progressed after the initial VAC treatment. The difference in MST between nonresponders and the others was significant. Results are compared with others reported for combinations of cytotoxic agents and radiotherapy. (7 Refs)

16. RESPONSE OF MURINE TUMOURS TO COMBINATIONS OF CCNU WITH MISONIDAZOLE AND AND OTHER RADIATION SENSITIZERS.

Siemann DW
Experimental Therapeutics Div., Univ. Rochester Cancer Center, Box 704, 601 Elmwood Ave., Rochester, NY, 14642
Br J Cancer; 45(2):272-281 1982

The effect of combinations of the conventional chemotherapeutic agent 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and nitroimidazole radiation sensitizers was evaluated in female C3H mice. Tumor response to single-agent or combination therapy was assessed in a tumor growth-delay assay. In the KHT sarcoma the simultaneous addition of misonidazole (MISO) was found to increase significantly the tumor growth delay resulting from CCNU treatment. The observed enhancement ratios (ER) increased with MISO dose, and ranged from 1.3 to 1.9 for sensitizer doses of 0.25-1.0 mg/g. The combination of CCNU and 1.0 or 0.5 mg/g MISO in the RIF-1 tumor or the MT-1 tumor produced ERs of approx 2.0 and 1.5 respectively. In the KHT sarcoma a series of other nitroimidazole sensitizers, including Ro-05-9963, SR-2555, SR-2508 and metronidazole (METRO), were also evaluated at equimolar doses (5 mmol/kg) in combination with a 20 mg/kg dose of CCNU. Unlike MISO, these compounds in general failed to enhance the CCNU cytotoxicity in this tumor model. However, SR-2508 did enhance the response of the RIF-1 tumor to large single doses of CCNU, though not as much as MISO. Normal tissue toxicity was determined using peripheral white blood cell (WBC) counts 3 days after treatment. CCNU doses of 10-50 mg/kg given either alone or in simultaneous combination with 0.5 or 1.0 mg/g MISO were studied. WBC toxicity increased with CCNU dose, but the addition of MISO at either dose did not significantly enhance this normal-tissue toxicity. (Author abstract) (39 Refs)

17. RESPONSE OF TWO MOUSE TUMOURS TO HYPERTHERMIA WITH CCNU OR MELPHALAN.

Joiner MC, Steel GG, Stephens TC
Gray Lab. of Cancer Res. Campaign, Mount Vernon Hosp., Northwood, Middlesex HA6 2RN, England
Br J Cancer; 45(1):17-26 1982

The in vivo response of B16 melanoma and Lewis lung carcinoma to combinations of hyperthermia and graded doses of lomustine (CCNU) or Melphalan was studied. To obtain dose-response curves and quantitive comparisons of different treatments, an agar-colony assay was used to measure survival of cells from excised tumors. For heating experiments, the use of two tumors per animal, one heated and one not, allowed all other factors to be kept constant. When tumors were immersed in a water-bath at 43 C for 1 h, thermal enhancement ratios (TER) measured from the slopes of the dose-response curves were up to 1.6 for CCNU and 2.4 for Melphalan. Direct heat killing of about 1 decade was seen for 1 h at 43 C. The anesthetic Saffan also enhanced drug cell kill; the largest Dose Modifying Factor (2.7) was measured for Melphalan in the Lewis lung tumor. The duration of heating, and waterbath temperature, both influenced the enhancement of cell killing by CCNU, as did the time of excision of tumors between 0 and 3 1/2 h after treatment. There was no difference in effect between 3 1/2 and 24 h. The interaction between heat and CCNU varied if the interval between them was altered. The maximum effect was found it the heat and drug were given in close sequence. (Author abstract) (14 Refs)

18. EFFECT OF CHLORAMBUCIL AND INDOMETHACIN ON GROWTH AND PROSTAGLANDIN LEVELS IN SENSITIVE AND RESISTANT WALKER CARCINOMA.

Tisdale MJ, Gibbs J, Dobrzanski RJ
Dept. Pharmacy, Univ. Aston Birmingham, Gosta Green, Birmingham B4 7ET, England
Chem Biol Interact; 39(2):221-230 1982

An analysis of the effect of combinations of chlorambucil and indomethacin or chlorambucil and prostaglandin E2 (PGE2) on the growth of alkylating agent sensitive and resistant Walker carcinoma in vitro has been made by the isobologram approach. Indomethacin alone acts as a growth inhibitor of the Walker carcinoma. High concentrations of indomethacin (5 ug/ml) act to inhibit the growth of the resistant line sub-additively with chlorambucil, whereas low concentrations act additively. For the sensitive line indomethacin acts either additively or supra-additively with chlorambucil at all concentrations employed. Both indomethacin and low concentrations of chlorambucil alone inhibit PGE2 secretion into the culture medium of both cell lines and an enhanced inhibition is seen with the combination. PGE2 itself acts as a growth inhibitor of both cell lines, although it causes greater growth inhibition of chlorambucil resistant Walker carcinoma (LD50 1.8 ug/ml) than of the sensitive line. This correlates with a greater PGE2 secretion capacity by the resistant cell line (40 pg PGE2/ml medium/10(5) cells for the resistant tumor and 17 pg PGE2/ml medium/10(5) cells for the sensitive tumor). Combinations of PGE2 with chlorambucil inhibit growth either additively or sub-additively. It seems unlikely that inhibition of PGE2 secretion is responsible for the interactive effects of chlorambucil and indomethacin, since growth inhibition produced by the combination is not reversed by PGE2 at any of the concentrations employed. Possible mechanisms of the interactive effects are discussed. (Author abstract) (18 Refs)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

19. NORADRENALINE AND ALPHA BLOCKERS IN DAUNOMYCIN CARDIOTOXICITY.

Soldani G, Del Tacca M, Bernardini C
Istituto di Farmacologia Medica, Universita di Pisa, Pisa, Italy
Clin Toxicol; 18(12):1435-1440 1981

Guinea pigs acutely treated with daunomycin (Daunorubicin) at 40 and 60 mg/kg body weight ip showed significantly elevated levels of noradrenaline in the heart. Electrocardiograms taken at these dosages showed electrical wave alteration consisting of a decrease or reversion of the T waves or an increase in wave voltage. Pretreatment with nicergoline (4 mg/kg, ip) or yohimbine (4 mg/kg, ip) failed to protect guinea pigs from daunomycin cardiotoxicity. (12 Refs)

20. COPPER- AND ZINC-CONTAINING SUPEROXIDE DISMUTASE, MANGANESE-CONTAINING SUPEROXIDE DISMUTASE, CATALASE, AND GLUTATHIONE PEROXIDASE IN NORMAL AND NEOPLASTIC HUMAN CELL LINES AND NORMAL HUMAN TISSUES.

Marklund SL, Westman NG, Lundgren E, Roos G
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Cancer Res; 42(5):1955-1961 1982

Copper- and zinc-containing superoxide dismutase, manganese-containing superoxide dismutase, catalase, and glutathione peroxidase form the primary enzymic defense against toxic oxygen reduction metabolites. Such metabolites have been implicated in the damage brought about by ionizing radiation, as well as in the effects of several cytostatic compounds. These enzymes were analyzed in 31 different human normal diploid and neoplastic cell lines and for comparison in 15 normal human tissues. The copper- and zinc-containing superoxide dismutase appeared to be slightly lower in malignant cell lines in general as compared to normal tissues. The content of manganese superoxide dismutase was more variable than the content of the copper- and zinc-containing enzyme. Contrary to what has been suggested before, this enzyme did not appear to be generally lower in malignant cells compared to normal cells. One cell line, of mesothelioma origin (P27), was extremely abundant in manganese-containing superoxide dismutase; the concentration was almost an order of magnitude larger than in the richest normal tissue. Catalase was very variable both among the normal tissues and among the malignant cells, whereas glutathione peroxidase was more evenly distributed. In neither case was a general difference between normal cells and tissues and malignant cells apparent. The myocardial damage brought about by doxorubicin has been linked to toxic oxygen metabolites; particularly, an effect on the glutathione system has been noted. The heat is one of the tissues which have a low concentration of enzymes which protect against hydroperoxides. However, the deviation from other tissues is probably not large enough to provide a full explanation for the high doxorubicin susceptibility. In the present survey, no obvious relationship between generally assumed resistance to ionizing radiation or to radical-producing drugs and cellular content of any of the enzymes could be demonstrated. (Author abstract) (66 Refs)

21. CARDIOTOXIC EFFECTS OF DOXORUBICIN WITH AND WITHOUT CARNITINE: USEFULNESS OF THE MOUSE MODEL IN ASSESSMENT.

Strohm GH, Payne CM, Alberts DS, Peng YM, Moon TE, Bahl JJ, Bressler R

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Arch Pathol Lab Med; 106(4):181-185 1982

A mouse model of long-term doxorubicin hydrochloride (adriamycin) toxicity, which demonstrated significantly longer survival when carnitine is administered simultaneously with doxorubicin, was evaluated by electron microscopic and biochemical study of cardiac muscle to correlate ultrastructural and metabolic changes with survival. One hundred Balb/C mice were randomly divided into four groups: control, carnitine, doxorubicin-carnitine, and doxorubicin alone. Significantly improved survival occurred in the doxorubicin-carnitine group when compared with the group receiving doxorubicin alone, in two separate experiments. However, there were no statistically significant differences in cardiac ultrastructure, carnitine concentration, or palmitate oxidation rates between treatment and control groups. The results indicate that although the mouse is useful for study of survival related to doxorubicin toxicity and combination and drug therapies, it does not seem to be suitable for evaluation of ultrastructural changes related to long-term doxorubicin cardiotoxicity. (Author abstract) (31 Refs)

22. PSYCHIATRIC ASPECTS OF CHEMOTHERAPY FOR CANCER.

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UCLA Cancer Cent Bull; 9(1):6 1982

Cancer chemotherapy can result in behavioral change, emotional stress, organic mental disorders, and affective disturbances. Severe depression, agitation, or seizure episodes with measured slow-wave electroencephalographic activity may also occur. Most psychiatric syndromes occur shortly after administration of a chemotherapeutic agent, are dose related, and are reversible on withdrawal of chemotherapy. Further studies concerning the psychiatric effects of chemotherapy are needed. (2 Refs)

23. SERIOUS TOXICITIES ASSOCIATED WITH CHEMOTHERAPY.

Friedman MA, Carter SK
Cancer Res. Inst., Univ. California, San Francisco, CA
Oncologic Emergencies. Yarbro JW and Bornstein RS, ed. New York, Grune and Stratton, Clinical Oncology Monographs, 430 pp., 1981.

Toxicities are described for the following chemotherapeutic agents: adriamycin and daunomycin (cardiac toxicity including electrocardiographic changes, heart enlargement, and congestive heart failure), bleomycin (cutaneous reactions including mouth ulcers, hyperpigmentation, thickening, and ulceration; pulmonary toxicity), androgens (fluid retention, hypercalcemia), estrogens (fluid retention, hypercalcemia, and thrombotic and phlebitic occurrences), L-asparaginase (hepatic and neurologic toxicities, allergic reactions), cyclophosphamide (chronic fibrotic lung disease, cardiotoxicity, and urinary tract toxicity), methotrexate (mucositis, bone marrow suppression and kidney, lung, liver, and nervous system toxicities), mithramycin (hypercalcemia, bleeding disorders, hepatotoxicity), nitrosoureas (bone marrow suppression, lung and kidney toxicities), cisplatinum (kidney toxicity, neurotoxicity, and allergic reactions), and vinca alkaloids (nervous system toxicity). (59 Refs)

24. EXPERIMENTAL STUDIES CONCERNING THE SIGNIFICANCE OF THE REFLUX DURING CHEMOPROPHYLAXIS AGAINST RECURRENCE CARCINOMA OF THE BLADDER.

Hautumm B, Birke F, Grauel H
Urologische Klinik, St. Antonius Hospital, 5180 Eschweiler, W. Germany
Therapiewoche; 32(5):515-516,519 1982

The effects of mitomycin C (MMC) and adriamycin (ADM) on renal urothelium during urinary reflux was studied in male white New Zealand SPF rabbits. Both kidneys of 29 rabbits were catheterized and test soln were instilled. MMC (0.5 mg in 1 ml NaCl soln) was instilled into both kidneys of 11 rabbits. ADM (2.0 mg in 1 ml NaCl soln) was instilled into both kidneys of 12 rabbits. Sterile NaCl soln was instilled into both kidneys of three rabbits. One rabbit received MMC into one kidney and NaCl into the other. One rabbit received ADM into one kidney and NaCl into the other. One rabbit received ADM into one kidney only. Instillations were retained in the kidney for 60 min and were repeated up to 3x at 24-hr intervals. Animals were killed at 1-4 days or 6 wk. No urothelial lesions were found in 27 kidney preparations with intact urothelium. Urothelial defects, accompanied by subepithelial inflammatory changes, were found in 15 ADM-treated kidneys, 11 MMC-treated kidneys, and 4 NaCl-treated kidneys. The degree of alteration was greater in ADM-treated kidneys than in those treated with MMC or NaCl. No pathological changes in renal cortex or medulla were noted. Results suggest that prophylactic treatment of bladder cancer with ADM or MMC in cases involving urinary reflux does not induce chemical nephritis. The experimental method was, however, not suitable for detection of minimal changes in the upper urinary tract. (13 Refs) (In GER)

25. UNORTHODOX METHODS OF TREATMENT FOR CANCER.

Brown HG
Community Cancer Control, 5800 Wilshire Blvd., Los Angeles, CA, 90036
Front Radiat Ther Oncol; 16:184-189 1982

Amygdalin (Laetrile) causes both acute and chronic cyanide poisoning. the quality of the amygdalin now available is very uneven and generally very poor. The 'metabolic diet' that is recommended as an adjunct to amygdalin ingestion is a high-bulk, low-calorie diet (cancer diets need a high-calorie, low-bulk diet), deficient in several essential nutrients (absorbable iron, vitamin B12, and calcium), and containing toxic quantities of other components. Freedom of choice should not mean that one can obtain a 'cancer remedy' which is neither effective nor safe. (2 Refs)

26. PROLIFERATIVE DEFECTS IN RENAL AND INTESTINAL EPITHELIUM AFTER CIS-DICHLORODIAMMINE PLATINUM (II).

Kovacs CJ, Braunschweiger PG, Schenken LL, Burholt DR
Radiation Oncology Lab., Dept. Radiology, Section Radiotherapy, Bowman Gray Sch. Medicine, Wake Forest Univ., Winston-Salem, NC, 27103
Br J Cancer; 45(2):286-294 1982

The effects of cis-dichlorodiammine platinum II (DDP) on the intestinal mucosa and the kidney were studied after single and multiple treatments with intervals of 7-45 days. After a single treatment, the jejunal epithelium underwent a transient interruption of cell proliferation followed by a hyperplastic recovery and return to control proliferative rate on Day 7. Subsequent treatments led to suboptimal recovery for all treatment intervals. In contrast, DDP induced a six-fold increase in [3H]dT incorporation in the kidney by Day 7 which remained high until Day 21, and returned to near-control values by Day 45. After a single DDP treatment, the 'recovery potential' of kidneys, measured by the proliferative response to folic-acid stress, demonstrated suboptimal proliferative reserve compartments for up to 45 days. The distinction between acute and delayed sensitivity to subsequent drug treatment was more apparent in the DDP-treated kidney than in the intestinal epithelium. (Author abstract) (28 Refs)

27. MECHANISM OF TOXICITY OF PLATINUM (II) COMPOUNDS IN REPAIR-DEFICIENT STRAINS OF ESCHERICHIA COLI.

Alazard R, Germanier M, Johnson NP
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Mutat Res; 93(2):327-337 1982

Three platinum compounds, cis-platinum diamino dichloride (cis-PDD), trans-platinum diamino dichloride (trans-PDD), and [Pt(dien)Cl] Cl (dien = H2N-CH2-CH2-NH-CH2-CH2-NH2), were studied in terms of survival experiments with 10 strains of Escherichia coli, platinum binding to DNA immediately after treatment, inhibition of DNA synthesis, and repair synthesis and toxicity of these compounds in wild-type and repair-deficient E coli strains. The three Pt compounds bind to E coli DNA in vivo. The cis- and trans-PDD exert their toxic effect by inhibition of DNA synthesis. Wild-type bacteria is able to survive by partially repairing these DNA lesions, but mutant strains cannot accomplish this repair. The lower toxicities of trans-PDD and [Pt(dien)Cl] Cl are not due to a low level of DNA binding or to a greater repair of the damaged DNA, suggesting that E coli replication is unimpaired by some Pt(II)-chloramine-DNA adducts. The relative toxicities of the three types of DNA damage appear to depend on the structure of Pt-DNA adducts as well as on the number of lesions. (21 Refs)

28. STUDIES OF DNA DAMAGE AND CELL DEATH IN EMBRYONIC LIMB BUDS INDUCED BY TERATOGENIC EXPOSURE TO CYCLOPHOSPHAMIDE.

Manson JM
Dept. Enviornmental Health, Univ. Cincinnati, Cincinnati, OH
Teratogenesis Carcinog Mutagen; 2(1):47-59 1982

DNA damage was measured in limb buds from mouse embryos exposed to cyclophosphamide (CP) in utero. Pregnant ICR mice were given 20 mg/kg CP ip on day 11 of pregnancy, and limb buds were taken from analysis at 1, 5, 24, 48, and 72 hr. This dose of CP resulted in 30% embryolethality, and 85% of the survivors had major forelimb malformations. DNA damage was determined by alkaline elution without prelabeled DNA and measured as retention on a filter. Total DNA content was analyzed from right forelimbs, alkali-labile DNA from left forelimbs. The CP caused a slight excess of necrosis at 5 hr and massive necrosis at 24, but not excess at 48 or 72 hr. There was a trend towards increasing DNA damage with time, with the greatest differences occurring at 48 and 72 hr. There was not a significant difference between mean retention values, but there was significantly increased variance in all retention values except at 1 hr. Results suggest that the CP treatment caused heritable DNA alterations in surviving cells. (17 Refs)

29. GERM CELL-SPECIFIC DECREASE OF ACROSOMAL PROTEOLYTIC ACTIVITY, SPERM MOTILITY, AND NUMBER IN MITOMYCIN C-TREATED MICE.

Ficsor G, Salama NM, Block KK, McIntire CL, Ginsberg LC
Dept. Biomedical Sciences, Western Michigan Univ., Kalamazoo, MI
Teratogenesis Carcinog Mutagen; 2(1):13-18 1982

The effects of an ip injection of mitomycin C (MC) on sperm count and motility, and acrosomal proteolytic activity were investigated in HA (ICR) albino mice. MIce were 10-12 wk old when injected with 5 mg/kg MC, and killed 1, 3, 5, 7, and 10 wk later, when the MC would have affected spermatozoa, spermatids, preleptotene-late spermatogonial cells, spermatogonium, or spermatogonial stem cells, respectively. Acrosomal proteolytic activity was determined by spreading a sperm suspension on a gel, incubating, fixing and staining, and observing individual sperm for a halo of unstained degraded protein, indicating activity. Sperm count and motility were similar to controls at 1, 3, and 10 wk after treatment,and significantly decreased at 5 and 7 wk. Acrosomal proteolytic activity was similar to controls at 1 and 3 wk, and decreased at 5, 7, and 10 wk. Testis wt was similar to controls at 1 and 10 wk, and significantly decreased at 3, 5, and 7 wk. It is proposed that MC effects on spermatogonial cells (7 and 10 wk) are mutational or developmental, while those on preleptotene or late spermatogonial cells (5 wk) are developmental. (19 Refs)

30. ADRIAMYCIN AND AUTOLOGOUS BONE MARROW TRANSPLANTATION. PRECLINICAL STUDIES IN DOGS.

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Blut; 44(2):115-120 1982

The toxicity of adriamycin (ADM) was investigated in 1-4 yr old Beagle and Labrador dogs (7.2-23.6 kg body wt) with regard to autologous bone marrow transplantation (BMT). Single dose of 1.5 mg/kg body wt (4 dogs) and 3.0 mg/kg body wt (8 dogs) ADM were administered iv during several min. Rapid administration induced a dose-dependent spontaneously reversible hypertension. Slow ADM administration (greater than 10 min) prevented the appearance of the cardiogenic shock. Diarrhea with or without vomiting was observed in all dogs. Three dogs which received 3.0 mg/kg ADM died after 4-5 days. Leukopenia (0-10,000/cubic mm) was observed in these dogs. Repeated administration of 1.5 mg/kg ADM after 14 days induced a less expressed gastrointestinal toxicity. Concentration of hemopoietic precursors (CFUc) and the DNA metabolism in the bone marrow decreased after 3 days of ADM administration and returned to normal levels after 10 days. Colony stimulating activity preceded the increase of CFUc. Cell fractions in S, G2, and M phase decreased after 3 days of ADM administration, increased after 10 days, and returned to normal levels on day 17 and 24. Fifteen dogs received total body irradiation (10 Gray units) and autologous BMT. One dog died of diarrhea after 3 days, and three dogs died of infection on day 7, 8, and 9 without recovery of blood counts. Results indicate that toxicity of ADM is not influenced by autologous BMT. (15 Refs) (In GER)

31. ACTIVATION OF AN ENDOGENOUS MOUSE TYPE C VIRUS BY UV-IRRADIATED MURINE CYTOMEGALOVIRUS.

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Int J Cancer; 29(4):459-464 1982

Infection of Kirsten sarcoma virus-transformed non-producer BALB-3T3 mouse cells with UV-irradiated mouse cytomegalovirus (MCMV) resulted in activation of a xenotropic Type C virus detected by infectious center formation in permissive rat or mink cells. The levels of Type C virus activated by MCMV were related to the UV dose applied. Unter optimal conditions the frequencies of activation varied from 3.0 to 8.0 x 10(-4). The capacity of MCMV to activate Type C virus was abolished by heat inactivation and by neutralization with specific antiserum against MCMV. Virus induction decreased under conditions of cell exposure to hydroxyurea or actinomycin D, inhibitors of DNA and RNA synthesis, respectively, with actinomycin D having a greater inhibitory effect. This suggests that both DNA and RNA synthesis are required for UV-MCMV induction of murine xenotropic virus. (Author abstract) (33 Refs)

32. OCULAR ABSORPTION AND TOXICITY OF A RADIOSENSITIZER AND ITS EFFECT ON HYPOXIC CELLS.

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Arch Ophthalmol; 100(3):468-471 1982

The recurrence of retinoblastoma after radiation treatment may be related to hypoxic cell radioresistance. Radiosensitizing drugs acting on hypoxic cells without affecting the responses of oxygenated cells could improve treatment of ocular tumors while minimizing complications of radiotherapy. A desmethyl derivative of misonidazole is as effective a radiosensitizer as misonidazole (as measured in vitro) and is better suited to ocular administration, since it is more soluble than misonidazole. We studied the ocular toxic effects of a desmethyl derivative of misonidazole after subconjunctival administration of 140 and 70 mg. The higher dose produced an intolerable ocular toxic effect, but at the lower dose, the toxic effect was moderate and reversible. We compared ocular pharmacokinetics of the desmethyl derivative of misonidazole after subconjunctival and intravenous (IV) injections. Subconjunctival administration yielded vitreous and anterior chamber concentrations of the radiosensitizer sufficient to produce a notable dose-modifying effect (as high as 1.8 in the anterior chamber and 1.25 in the vitreous at 70-mg doses). In contrast, even at doses of 140 mg, IV injections of the desmethyl derivative of misonidazole did not result in therapeutically useful ocular levels. (Author abstract) (15 Refs)

33. CYTOTOXIC-THERAPY-INDUCED VOMITING IS MEDIATED VIA ENKEPHALIN PATHWAYS.

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Lancet; 1(8274):714-716 1982

Cytotoxic drugs may exert their emetic effects via inhibition of enzymes that break down neurotransmitters in the area postrema. The differences between emetic effects of cytotoxic drugs can be related to whether they act on DNA, RNA, or protein synthesis. Enzymes that degrade enkephalins are a potential target. Most anti-emetics are dopamine antagonists and are only marginally effective. Opiates are emetic and many of their effects are mediated via dopamine systems. Opiates also have anti-emetic effects that may be mediated via a medullary anti-emetic center. Inhibition of enkephalin production in this center may potentiate effects at the area postrema. Opiates and selective antagonists should be assessed for anti-emetic activity. (Author abstract) (42 Refs)

34. EXPRESSION OF HERPES SIMPLEX VIRUS TYPE-COMMON SURFACE ANTIGENS IN CLONAL CELLS OF AN HSV TYPE 2-TRANSFORMED LINE: EFFECT OF ADRIAMYCIN.

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Microbiol Immunol; 25(12):1265-1278 1981

The expression of herpes simplex virus (HSV) type-common surface antigen (CSA) was studied in a representative cell clone (155-4-03) of hamster cell line 155-4 transformed by HSV type 2. HSV-CSA was detected by the indirect immunofluorescence test. Expression of HSV-CSA was enhanced by treatment with inhibitors of RNA synthesis (adriamycin [ADM] and daunomycin) but not by inhibitors of DNA synthesis (2-iododeoxyuridine, bleomycin, mitomycin C and cytosine arabinoside), even though all of these agents decreased the number of viable cells in culture to about the same extent. Addition of puromycin or 2-deoxy-D-glucose to ADM markedly suppressed expression of CSA, indicating that both protein synthesis and glycosylation are necessary. ADM enhanced expression of CSA was sensitive to protease inhibitors (antipain and p-nitrophenyl-p'-guanidinobenzoate) and procaine. Procaine affects the organization of the cytoskeletal system (microfilaments and microtubules) in animal cells and also inhibits trypsin. Low concentrations of ADM (0.1 ug/ml) and actinomycin D (0.5 ug/ml) increased CSA expression in an additive manner, while optimal concentrations of each (0.25 and 2.0 ug/ml, respectively) did not. These findings indicate that the two drugs enhance CSA expression in the clone by a common mechanism. (40 Refs)

PHARMACOKINETICS OF ANTITUMOR AGENTS

35. EFFECTS OF PARTIALLY THIOLATED POLYCYTIDYLIC ACID AND LIPOSOMES ON IN VITRO COLONY-FORMING CELLS OF LEUKEMIC MICE.

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Cancer Res; 42(5):1740-1743 1982

Partially thiolated polycytidylic acid (MPC), an antileukemic agent, when administered to leukemic RF/UN mice inhibited the clonogenicity of bone marrow progenitor cells in a time- and dose-dependent manner. The effect of a single dose of MPC disappeared within 40 hr due to the rapid degradation of this compound in mice. When MPC was encapsulated in liposomes before injection, its activity at 19 hr after inoculation was similar to that of free MPC. The inhibitory effect of this liposome-MPC complex, however, persisted for at least 40 hr, indicating that the MPC was protected from hydrolysis by the nucleases present in blood. Drug-free liposomes increased the number of clonogenic progenitor cells, whereas a mixture of plain liposomes and MPC decreased the number of clonogenic cells to a greater extent than did MPC alone or MPC within liposomes. A possible explantation for these observations is that the liposomes per se altered the clearance function of the reticuloendothelial system and competed with MPC for uptake by the reticuloendothelial system cells, thereby resulting in increased plasma levels of MPC which in turn resulted in greater killing of the target cells. (Author abstract) (23 Refs)

36. INFLUENCE OF TETRAHYDROURIDINE ON THE PHARMACOKINETICS OF INTRATHECALLY ADMINISTERED 1-BETA-D-ARABINOFURANOSYLCYTOSINE.

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Cancer Res; 42(5):1736-1739 1982

Tetrahydrouridine (THU), a potent inhibitor of cytidine deaminase, has been shown to increase the antitumor activity of 1-beta-D-arabinofuranosylcytosine (ara-C) both in vitro and in vivo. In initial studies, which examined the cerebrospinal fluid (CSF) pharmacokinetics of intrathecally (it) administered THU, the drug was found to be slowly cleared from the CSF with alpha and beta half-lives of 1 and 8 hr, respectively. In subsequent experiments, both iv pretreatment with THU and concomitant it injection of THU were found to retard the disappearance of it ara-C from the CSF, although the effect of it THU was more profound. Ara-C given alone was cleared from CSF with alpha and beta half-lives of 27.5 +-6.7 and 115.6 +-0.4 (SD) min, respectively. Pretreatment with iv THU resulted in alpha and beta half-lives of 10.4 +-1.5 and 85.7 +-11.1, respectively, whereas concomitant administration of it THU resulted in a single half-life of 96 +-0.7. The mean calculated clearance rates for ara-C alone, ara-C plus iv THU, and ara-C plus it THU were 7.5, 6.2, and 4.2 ml/hr, respectively. This effect appeared to be primarily due to THU inhibition of ara-C deamination, since a decrease in formation of 1-beta-arabinofuranosyluracil in the CSF was observed when ara-C was given in the presence of THU (either it or iv). No acute neurotoxicity was noted after administration of either it THU alone or it THU with ara-C. The ability of THU to alter CSF ara-C pharmacokinetics may have potential therapeutic value. (Author abstract) (20 Refs)

37. PHARMACOLOGY AND TOXICITY OF A POTENT 'NONCLASSICAL' 2,4-DIAMINO QUINAZOLINE FOLATE ANTAGONIST, TRIMETREXATE, IN NORMAL DOGS.

Weir EC, Cashmore AR, Dreyer RN, Graham ML, Hsiao N, Moroson BA, Sawicki WL, Bertino JR
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Cancer Res; 42(5):1696-1702 1982

The pharmacology of trimetrexate (JB-11, NSC 249008, 2,4-diamino-5-methyl-6-[(2,4,5 trimethoxyanilino)methyl]quinazoline), an antitumor agent effective against several mouse tumors, was studied in normal dogs. A high-performance liquid chromatographic technique with electrochemical detection, dihydrofolate reductase inhibition assay, and 14C-labeled drug were used to measure plasma disappearance, tissue distribution, excretion, and metabolism of the drug at doses from 0.5 to 6 mg/kg. Doses of 2 mg/kg were well tolerated without toxicity. Higher doses (3 to 6 mg/kg) produced mainly intestinal toxicity without significant hematological or liver abnormalities. The 6-mg/kg dose caused severe bloody diarrhea. After administration of 3 mg/kg, plasma concentrations of trimetrexate were 1 uM and were equal to or greater than 0.1 uM at 1 and 24 hr, respectively. The predominant pharmacokinetics of trimetrexate plasma disappearance was an elimination phase with a t 1/2 of 3.5 hr. Concentrations in the cerebrospinal fluid were 2 to 5% of that in plasma and were maximum within 1 to 2 hr after iv administration. Highest tissue concentrations of drug were measured in liver and kidney; lowest were found in brain and lung. A dose equivalent to 3 mg/kg in humans (on a sq m basis) should produce adequate plasma concentrations (greater than 0.1 uM) for therapeutic effects. (Author abstract) (13 Refs)

38. TISSUE DISTRIBUTION AND ANTITUMOR EFFECT OF LIPOSOME-ENTRAPPED DOXORUBICIN (ADRIAMYCIN) IN EHRLICH SOLID TUMOR-BEARING MOUSE.

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Acta Med Okayama; 35(6):395-405 1981

The usefulness of liposomes (in neutral, positively and negatively charged forms) as a carrier for adriamycin (ADM) was studied by examining the distribution of ADM and related fluorescent compounds in Ehrlich solid tumor-bearing mice. The mice were given free or liposome-entrapped ADM intraperitoneally. The distribution of ADM and related fluorescent compounds between the administration of the free form and liposome-entrapped form was measured by high-performance liquid chromatography: The distribution was dependent on the form of the liposomes. The amounts of ADM and its metabolites in the mouse serum 20 min after administration of neutral-liposome-entrapped ADM were 10x those after the administration of free ADM, 6x those after the administration of a negatively charged form, and 3.5x those in the administration of positively charged form. There was no marked difference in the concentrations of these compounds 5 hr after administration. The concentration of these compounds in the liver 60 min after administration of each liposome-entrapped form of ADM were in inverse correlation with the concentrations in the serum obtained at 20 min after administration. Total concentrations of ADM and its metabolites in the tumors 20 min after administration of each entrapped form of ADM were 4-5 x that in administration of free ADM after 20 min. There were no marked differences in the concentration of ADM for administration of the various liposome forms. Statistically significant decreases in mean tumor weight were seen in the groups given neutral, positively and negatively charged liposome-entrapped forms compared to corresponding control groups given with free ADM. (Author abstract) (25 Refs)

39. CHARACTERIZATION, TOXICITY AND THERAPEUTIC EFFICACY OF ADRIAMYCIN ENCAPSULATED IN LIPOSOMES.

Olson F, Mayhew E, Maslow D, Rustum Y, Szoka F
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Eur J Cancer Clin Oncol; 18(2):167-176 1982

The inherent toxicities of drug-free liposomes were compared. Positively charged liposomes were more toxic in vitro (chick heart cells) and in vivo (5-fold reduction in LD50 in mice) than neutral or negatively charged liposomes. Based on these findings, adriamycin was encapsulated in negatively charged liposomes (PG: PC: Chol-1:4:5), sequentially extruded through polycarbonate membranes (to 0.2 um pore size) and purified by exhaustive dialysis. This preparation had a mean vesicle diameter of 0.24 um and was stable in serum (24 hr drug retention of 85%). As compared with free drug, liposome-encapsulated adriamycin was less toxic in vitro to chick heart cells. In mice, adriamycin displayed short- (4-14 day) and long- (45-70 day) term toxicity. Encapsulating adriamycin increased both short- (20-50 mg/kg) and long- (10-15 mg/kg to 25-30 mg/kg) term LD50 levels. As compared with free drug, administering encapsulated adriamycin in vivo reduced the incidence of cardiac histopathologic lesions at 20 and 40 mg/kg. Compared in vivo, plasma levels of liposome-encapsulated adriamycin were 2/3-fold higher than free drug up to 24 hr post drug administration. Cardiac uptake of adriamycin was reduced two-fold (conc x time value for 48 hr) following encapsulated drug administration. Encapsulating adriamycin in liposomes did not alter its therapeutic effect against L1210 leukemic cells in vivo. (Author abstract) (22 Refs)

40. UPTAKE, EFFLUX, AND HYDROLYSIS OF ACLACINOMYCIN A IN FRIEND LEUKEMIA CELLS.

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Cancer Res; 42(5):1950-1954 1982

The kinetics of uptake by cells and nuclear incorporation of aclacinomycin A was studied in Friend leukemia cells. It was shown that uptake is a very rapid process. The intracellular concentration is maximum in 10 min and mainly (about 75%) localized in the nucleus. Most of the incorporated drug will disappear from the cell by a two-step mechanism: (a) efflux from the nucleus to the cytoplasm; and (b) deglycosidation at C-7 to the alkavinone form in the cytoplasmic fraction. The cellular uptake was temperature dependent but was not prevented by sodium azide treatment. We assumed, therefore, that it is related to the composition and to the dynamic structure of the cell surface membrane. Nuclear outward transport and deglycosidation were inhibited by sodium azide and low temperatures; this suggests that they are regulated by an active transport process and by an enzymatic activity, respectively. (Author abstract) (21 Refs)

41. RECEPTOR-DEPENDENT ANTIPROLIFERATIVE EFFECTS OF CORTICOSTEROIDS IN RADIATION-INDUCED FIBROSARCOMAS AND IMPLICATIONS FOR SEQUENTIAL THERAPY.

Braunschweiger PG, Ting HL, Schiffer LM
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Cancer Res; 42(5):1686-1691 1982

Competitive binding studies with [3H]dexamethasone and Scatchard analysis demonstrated a single class of high-affinity, low-capacity glucocorticoid receptor sites in 105,000 x g cytosols from radiation-induced fibrosarcomas. In vivo, both dexamethasone (DEX) and methylprednisolone treatments resulted in dose-dependent inhibition of tumor growth and cell proliferation. Changes in the sensitivity of the clonogenic cell population to 3 mM hydroxyurea were used to assess changes in the clonogenic cell proliferation during and after treatments with DEX or methylprednisolone. Neither methylprednisolone nor DEX given every 12 hr for three doses resulted in significant cell kill in the clonogenic fraction. However, changes in the hydroxyurea sensitivity of the clonogenic population after cessation of DEX treatments indicated G1 cell cycle progression delay with transient enrichment of S-phase clonogenic cells 24 to 48 hr after cessation of DEX treatments. The duration of the DEX-induced progression delay and the timing of maximal S-phase cellularity after DEX was directly correlated with the level of glucocorticoid receptors in the treated tumors. Using regrowth delay to assess the efficacy of kinetically directed sequential chemotherapy, the effectiveness of vincristine, given after DEX, was highly sequence dependent, with the most effective treatment interval being coincident with maximal S-phase clonogenic fraction. Other studies indicated that the effectiveness of cyclophosphamide could also be increased by time sequencing after DEX. (Author abstract) (46 Refs)

42. INTRACEREBRAL CHEMOTHERAPY: CHRONIC MICROINFUSION OF CISPLATIN.

Kroin JS, Penn RD, Sklar F, Neuwelt EA
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Neurosurgery; 10(3):349-354 1982

Chronic intracerebral microperfusion of cisplatin into the extracellular space of the brain of normal Wistar rats was investigated. Small stainless steel cannulas were connected to osmotic minipumps and stereotactically placed into the midline cerebellum or frontal cortex. Cisplatin was pumped into the brain at a rate of 0.9 ug/hr for periods up to 1 wk. Brain tissue was analyzed for total platinum content at 1-mm intervals from the cannula tip. In three rats in which cisplatin was infused for 150-160 hr, the amount of drug remaining ranged between 26 and 26.8% of the estimated amount of drug pumped. In a fourth rat with infusion for 100 hr, the amount of drug remaining was 27.4%. At 5 mm from the injection source the platinum concentration was greater than 2 nanog/mg of tissue wet wt in either direction. Concentrations were considerable near the cannula. When pieces of brain at greater distances from the cannula site were analyzed, no detectable platinum was observed. In comparison, no detectable levels of platinum were found in the brain 2 hr after iv injection of cisplatin (5 mg/kg), while plasma levels were near 1 ug/ml at the time of death. It is estimated that one cannula would be sufficient to treat a 1-cm tumor or a larger tumor that could be surgically reduced. A multiple cannula system would be appropriate for inoperable tumors up to 2 cm in diameter. For larger tumors, this system would not produce high enough drug levels. Microperfusion can be used to attain adequate and sustained drug levels over a considerable region of tissues without the problems of systemic toxicity. (39 Refs)

43. TAMOXIFEN ANTIESTROGENS. A COMPARISON OF THE ACTIVITY, PHARMACOKINETICS, AND METABOLIC ACTIVATION OF THE CIS AND TRANS ISOMERS OF TAMOXIFEN.

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J Steroid Biochem; 16(1):1-13 1982

Interaction of tritium-labeled cis and trans isomers of tamoxifen with target tissues was studied, and their pharmacokinetics and metabolism were compared. Observations in immature female Holtzman rats confirmed that the cis isomer is a full estrogen agonist in terms of uterine weight gain but that the trans isomer is both a partial agonist and an antagonist. Both isomers were weak stimulators of uterine peroxidase, but they differed in their ability to antagonize estrogen-stimulated uterine peroxidase: only trans-tamoxifen achieved significant antagonism. After rats were given 5-ug doses of 3H-trans-tamoxifen, polar metabolites accumulated in the uterine nucleus. After administration of the cis isomer, no accumulation of the corresponding metabolites occurred; instead, a small amount of metabolite with polarity between that of cis-tamoxifen and trans-hydroxytamoxifen appeared. Results of in vitro incubations with rat liver microsomes indicated that N-demthylation and hydroxylation of both isomers took place. Hydroxylation produced compounds with substantially increased affinity for the receptor, whereas N-demethylation had only a slight, if any, effect on the inhibitor. Results indicated that significant differences exist in the pattern of metabolites of cis and trans tamoxifen in the uterus; these differences apparently result from differences in affinity of cis and trans isomers of certain metabolites for the estrogen receptor. (29 Refs)

44. COMPARATIVE UPTAKE OF ADRIAMYCIN AND DAUNORUBICIN IN SENSITIVE AND RESISTANT FRIEND LEUKEMIA CELLS MEASURED BY FLOW CYTOMETRY.

Tapiero H, Fourcade A, Vaigot P, Farhi JJ
Departement de Pharmacologie Cellulaire et Moleculaire, Unite Simone et Cino Del Duca de Pharmacologie Humaine de Cancers, Institut de Cancerologie et d'Immunogenetique (INSERM U-50), Hopital Paul-Brousse, 14, avenue Paul Vaillant Couturier, 94804-Villejuif, France
Cytometry; 2(5):298-302 1982

The fluorescent intensity of adriamycin (ADM) and daunorubicin (DNR) on a single cell level was studied in sensitive and resistant Friend leukemia cells (FLC) derived from a clone of Friend virus transformed cells 745A. The uptake of ADM and DNR in FLC was analyzed by incubating 10(7) cells in a growth medium containing increasing amounts of ADM or DNR. The spontaneous fluorescence of untreated cells showed a single narrow peak whose position varied with the sensitivity of measurements. The fluorescence intensity was related to the drug concentration. Distribution profiles resulting from the exposure of FLC to 0, 1, 3, 10, and 30 ug ADM/ml are presented. When cells were incubated under the same conditions with DNR, higher fluorescence values were observed. The exposure of cells to ADM and to DNR in the presence of sodium azide (2 x 10(-2) M) did not affect the distribution of fluorescence peaks. Distribution of peaks changed after incubation at 37 C, 20 C, or 4 C. Incorporation into isolated nuclei was not affected by low temperature. Sublines of FLC resistant to ADM and DNR were obtained by continuous exposure to increasing concentrations of each drug over a period of 9 mo and maintained at 1 ug/ml of ADM and DNR for 3 mo. Cross resistance between these two sublines was observed. Exposure of these sublines to ADM and DNR showed that the mean cellular fluorescence was related to the initial concentration of drugs but at lower values than in sensitive cells. Resistant cells exposed to 10 ug DNR/ml led to a heterogeneous fluorescence distribution as compared to ADM exposed cells. (30 Refs)

45. EFFECTS OF O2 ON THE REACTIONS OF ACTIVATED BLEOMYCIN.

Burger RM, Peisach J, Horwitz SB
Dept. Molecular Pharmacology, Molecular Biology and Cell Biology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
J Biol Chem; 257(7):3372-3375 1982

The antitumor drug, bleomycin, interacts with either Fe(II) and O2 or Fe(III) and H2O2 to form an activated complex which attacks DNA. Under aerobic conditions, both reactions yield similar quantities of free bases and products consisting of base plus deoxyribose carbon atoms 1 to 3. Under anaerobic conditions, activated bleomycin releases only free base. The yield of free base is the same under aerobic or anaerobic conditions, provided DNA is furnished in excess. When the DNA concentration is limiting, more base is released under anaerobic than under aerobic conditions. Drug self-destruction proceeds as quickly and completely in the presence or absence of O2. (Author abstract) (15 Refs)

46. BASIC RESEARCH ON CHEMOTHERAPY UTILIZING MAGNETISM. V. PREPARATION, PROPERTIES, AND PHARMACOKINETICS OF MICROCAPSULES ENCASING MAGNETIC PARTICLES AND MITOMYCIN C.

Kato T, Nemoto R, Mori H, Abe R, Unno K, Goto A, Murota H, Harada M, Kawamura K, Homma M
Dept. Urology, Akita Univ. Sch. Medicine, Hondo, Akita 010, Japan
Nippon Gan Chiryo Gakkai Shi; 16(7):1351-1357 1981

A new type of ferromagnetic microcapsule encasing both mitomycin C (MMC) and ferrite particles within an ethylcellulose capsule was reported. In the past, ferromagnetic microcapsules containing MMC were made from capsules that had external surfaces on which the ferrite particles were attached. Although the magnetic induction of these capsules was adequate to perform selective chemotherapy, the quantity of ferrite particles that could be used was fixed. With the new method, the ratio of ferrite particles to drug could be varied, and the coarseness of the microcapsule surface could be reduced. Based on tests on the magnetism of microcapsules containing different ratios of ferrite particles:lactose, the optimum ratio of ferrite particle:MMC was determined to be 1:0.5. The size of the microcapsules was 250 +-43 micrometer/100 capsules. Toxicity of the new ferromagnetic MMC microcapsules was studied in female Donryu rats, and pharmacokinetics was studied in Japanese white rabbits. Results of the toxicity studies suggested that the ferromagnetic MMC microcapsules and the materials they were composed of were safe. Results of the pharmacokinetic studies indicated that magnetically-controlled intravesicular injection of the MMC microcapsules enhanced absorption of the MMC in the bladder tissue of the rabbits. These results suggested the feasibility and effectiveness of selective chemotherapy using the ferromagnetic MMC microcapsules. (13 Refs) (In JPN)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

47. LYSINE AND ORNITHINE ANALOGUES OF METHOTREXATE AS INHIBITORS OF DIHYDROFOLATE REDUCTASE.

Kempton RJ, Black AM, Anstead GM, Kumar AA, Blankenship DT, Freisheim JH
Dept. Physical Sciences, Northern Kentucky Univ., Highland Heights, KY, 41076
J Med Chem; 25(4):475-477 1982

The ornithine (6a) and lysine (6b) analogues of methotrexate (1) have been synthesized via condensation of 4-amino-4-deoxy-N10-methylpteroic acid (2) with N-delta-carbobenzoxy-L-ornithine tert-butyl ester (3a) and N-epsilon-carbobenzoxy-L-lysine tert-butyl ester (3b), respectively. Removal of the protecting groups gave 6a and 6b. Compounds 6a and 6b and their precursor Cbz acids (5a and 5b) show significant inhibition of dihydrofolate reductase. (Author abstract) (18 Refs)

48. INHIBITION OF GROWTH OF HUMAN CANCERS BY EXTRACTS FROM TRICHOPHYTON VERRUCOSUM.

Floersheim GL, Looser R, Grundmann HP, Meyer JC
Lab. Transplantation Biology, Dept. Surgery, Kantonsspital, Hebelstrasse 20, 4031 Basle, Switzerland
Lancet; 1(8274):708-710 1982

Lyophilized extracts from cultured dermatophytes were injected into mice carrying rapidly proliferating xenografts of a human Ewing sarcoma or a human colon carcinoma. Extracts from strains of Trichophyton verrucosum greatly inhibited the growth of both tumors. There were no overt signs of toxicity. (Author abstract) (15 Refs)

49. TOXICITY AND ANTICANCER ACTIVITY OF A NEW TRIAZINE ANTIFOLATE (NSC 127755).

Corbett TH, Leopold WR, Dykes DJ, Roberts BJ, Griswold DP, Schabel FM
Southern Res. Inst., Birmingham, AL, 35255
Cancer Res; 42(5):1707-1715 1982

A new triazine folate antagonist 3-chloro-4- *4- 2-chloro-4-*[*4,6-diamino-2,2-dimethyl-s triazin-1(2H)-yl*]*phenyl* butyl benzenesulfonyl fluoride compounded with ethanesulfonic acid (1:1) (NSC 127755), was highly active against four transplantable colon adenocarcinomas (36, 38, 10/A, 12/A) and the Dunning murine ovarian tumor M5076. Treatment schedule studies indicated that a prolonged time of exposure provided optimum antitumor activity for the compound. The combination of NSC 127755 plus 4-amino-1-[5-O-(1-oxohexadecyl)-beta-D arabinofuranosyl]-2(1H)- pyrimidinone (palmO-ara-C, NSC 135962) was found to have therapeutic synergism against grossly evident colon adenocarcinoma 36. (Author abstract) (19 Refs)

50. ALKYLATING DERIVATIVE OF GLUTARIC ACID WITH ANTITUMOUR PROPERTIES.

Stoychkov JN, Astardjieva ZL, Demireva ZY
Oncological Res. Inst., Medical Acad., 1156 Sofia, Bulgaria
Dokl Bolg Akad Nauk; 34(9):1323-1325 1981

Mean survival in DBA/2 mice and 210 hybrids of BD2F1 and CD2F1 mice of both sexes following ip injection of 10(5) L1210 leukemia cells was determined following ip administration of NIO 7901, an alkylating derivative of glutaric acid. A single injection of NIO 7901 (100-250 mg/kg) prolonged the lifespan of tumor-bearing DBA/2 mice by greater than 125%. A dose-response relationship was observed. Hybrid mice were more sensitive to the antitumor effects of NIO 7901. Intermittent injection of NIO 7901 was more effective than single injection. (3 Refs)

51. ACTIVITY OF 3BETA-HYDROXY-13ALPHA-AMINO-13,17-SECO-5-5A-1 ANDROSTANE-17-OIC-13,17-LACTAM(P-(BIS(2 CHLOROETHYL)AMINO)-PHENYL)ACETATE (NSC 290205) IN MURINE SOLID TUMORS.

Catsoulacos P, Wampler GL
Dept. Chemistry, Greek Atomic Energy Commission, Nuclear Res. Center 'Demokritos', Aghia Paraskevi, Attiki, Greece
Oncology; 39(2):109-112 1982

The modified steroidal alkylating agent, 3beta-hydroxy-13alpha-amino-13,17-seco-5alpha androstane-17-oic-13,17-lactam[p-[bis(2 chloroethyl)amino]-phenyl]acetate showed excellent activity in treatment of three murine solid tumors. Colon 26-bearing CD2F1 mice lived twice as long as controls with tumor free survivors at the end of the 70-day observation period. CD8F1 mammary tumor growth was suppressed greater than 90% compared to controls. B16 melanoma-bearing B6D2F1 mice lived 50% longer than controls. This agent had previously been shown to be active in treatment of the Theagenion-Bahner angiosarcoma, the T8 Guerin tumor, L1210 leukemia and P388 leukemia. (Author abstract) (26 Refs)

52. EX VIVO HEMODIALYSIS CULTURE SYSTEM FOR ASSESSING THE ACTIVITY OF CANCER CHEMOTHERAPEUTIC AGENTS.

Quarles JM, Morris NG, Leibovitz A
Dept. Medical Microbiology and Immunology, Coll. Medicine, Texas A and M Univ., College Station, TX, 77843
In Vitro; 18(2):165-172 1982

An ex vivo culture system was developed for assessing the activity of cancer chemotherapeutic agents against tumor cells. The system utilizes artificial capillary culture units and the technique of hemodialysis to expose tumor cells to a chemotherapeutic drug and its metabolites following injection of the drug into an experimental animal. This ex vivo culture system was used to test the activity of 5-fluorouracil (5-FU) against four human colorectal adenocarcinoma cell lines (SW 403, SW 480, SW 620, and SW 707). Cell killing by 5-FU or its metabolites in blood dialysate following intravenous injection was measured by determining colony formation of cells attached to plastic and suspended in 0.3% agar after short-term exposures of 1 to 2 hr. The technique was shown to discriminate between the sensitivities of these cell lines and the respective sensitivities to the drug were reproducible. Kinetics of drug clearance from the host animal's blood were shown to be similar to that in humans. The results suggest the system may be useful for testing diverse drugs, including those requiring metabolic activation, against a variety of types of tumor cells. (Author abstract) (44 Refs)

53. EFFECT OF ERGOT ALKALOIDS ON GROWTH OF MAMMARY GLAND CANCER IN MICE AND RATS.

Lagova ND, Ird EA, Chernov VA
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(1):73-74,76 1982

The antitumor efficacy of synthesized ergot alkaloids (EA) was studied in random-bred rats and CBA mice with transplanted mammary gland carcinoma. Of four EA tested, D-6-methyl-8-cyanomethylergolin alone reduced the yield of multiple breast tumors but did not affect the av latent period of tumor development. (8 Refs) (In RUS)

54. STUDIES ON THE ANTITUMOR ACTIVITY OF FUSOBACTERIUM NUCLEATUM STRAIN KO-31.

Tamai K, Nakao J, Takematsu K, Nakagawa K
Clinic Dento-Oral Surgery, Kanazawa Univ. Sch. Medicine, Kanazawa, Ishikawa 920, Japan
Microbiol Immunol; 26(2):163-165 1982

The antitumor activity of a culture supernatant fluid of Fusobacterium nucleatum strain KO-31 was investigated in ICR mice bearing Ehrlich ascites carcinoma. Mice were injected with a carcinoma cell suspension containing 8.0-12.0 x 10(6) cells/ml ip. Beginning 2 days later, a 0.5 ml dose of test sample was given ip daily for 7 days. The mice were observed for 60 days and the antitumor activity [expressed as T/C(%) = (survival days of treated group divided by survival days of control group) x 100] was determined. The T/C(%) of mice treated with culture supernatant fluid was 206.7, compared with 103.0 for control mice. In several repeats of the same experiment, greater than 80% of mice inoculated with cancer cells survived when treated with the culture supernatant fluid. Dialysis or heating at 100 C for 10 min had no effect on the antitumor activity of the culture supernatant fluid. Cell extract from the same strain of F nucleatum showed no antitumor effect in mice bearing carcinoma. The antitumor substance may be a kind of lipopolysaccharide rather than a protein, evidenced by its heat stability. (2 Refs)

55. MULLERIAN INHIBITING SUBSTANCE INHIBITS COLONY GROWTH OF A HUMAN OVARIAN CARCINOMA CELL LINE.

Fuller AF, Guy S, Budzik GP, Donahoe PK
(c/o Donohoe) Pediatric Surgical Res. Lab., Massachusetts General Hosp., Boston, MA, 02114
J Clin Endocrinol Metab; 54(5):1051-1055 1982

Mullerian inhibiting substance (MIS), a fetal testicular product which causes regression of the Mullerian duct in the male mammalian embryo, is being evaluated as an inhibitor of genital tract tumors. The present study demonstrates in a clonogenic soft agar assay that biologically active MIS inhibits the growth of a human ovarian carcinoma cell line (HOC-21) in a dose-dependent manner when compared to phosphate-buffered saline medium controls, heat-inactivated MIS, or biochemical fractions which lack biological activity (p less than 0.05). (Author abstract) (13 Refs)

56. ISOLATION AND CHARACTERIZATION OF A CHLAMYDOMONAS L-ASPARAGINASE.

Paul JH
Environmental Sciences Div., Code 4354, Naval Res. Lab., Washington, DC, 20375
Biochem J; 203(1):109-115 1982

An L-asparaginase (EC 3.5.1.1) specific for L-asparagine has been purified from a marine Chlamydomonas species, the first such enzyme to be purified from a microalga. The purified enzyme (mol wt 275,000) possessed a Km for asparagine of 1.34 x 10(-4) M and showed limited antitumor activity in an antilymphoma assay in vivo. Properties of the enzyme are contrasted with those of asparaginases from prokaryotic and eukaryotic sources. (Author abstract) (32 Refs)

57. CYTOSTATIC EFFECT OF CERTAIN SEMISYNTHETIC DERIVATIVES OF CARMINOMYCIN.

Volkolupova OP, Makukho LV
All-Union Res. Inst. Screening for New Antibiotics, Moscow, USSR
Antibiotiki; 27(2):145-147 1982

The cytostatic effect of six semisynthetic derivatives of carminomycin (CM) was studied in cultured cells of murine lymphadenoma NK/Ly. The antitumor activity was estimated by the inhibition of 3H-thymidine incorporation. All six derivatives were less active than CM. (11 Refs) (In RUS)

58. MULTIPLE FORMS AND INHIBITORS OF URIDINE-CYTIDINE KINASE IN NEOPLASTIC CELLS.

Ahmed NK
Div. Biochemical and Clinical Pharmacology, St. Jude Children's Res. Hosp., Memphis, TN
Int J Biochem; 14(4):259-262 1982

Two isozymes of uridine-cytidine kinase, a rate-limiting enzyme in the salvage pathway for pyrimidine nucleotide biosysnthesis, were demonstrated in both mouse L1210 ascites leukemia and human malignant lymphoma cells by isoelectric focusing and Sepharose 6B column chromatography. Eleven compounds were tested in vitro for their ability to inhibit the uridine-cytidine kinase-catalyzed phosphorylation of uridine by ATP in kinase preparations from L1210 and human 6410 leukemia cells. The compounds tested were: 5-iodouridine, 5'-iodo-5'deoxyuridine, 5-bromouridine, 5-chlorouridine, 5-cyanouridine, 6-aminocytidine, 4-thiouridine, 5'-azido-5'-deoxycytidine, 5'-azido-5'-deoxyuridine, 5'-O-nitrouridine, and 5'-O-nitrofluorouridine. The last four compounds were effective inhibitors of the enzyme from both cell types. While various compounds are known to inhibit the de novo pathway for uridine monophosphate (UMP), none have been available as inhibitors of the salvage pathway or of uridine-cytidine kinase specifically. The 5'-azido and 5'-O-nitro analogs may have chemotherapeutic potential either administered singly or in combination with inhibitors of the de novo pathway to UMP. (14 Refs)

59. ADRIAMYCIN ANALOGUES. PREPARATION OF 9,10-ANHYDRODAUNORUBICIN, 9-10-ANHYDROADRIAMYCIN, AND SOME RELATED COMPOUNDS.

Potti G, Israel M
(c/o Israel) Div. Pharmacology, Sidney Farber Cancer Inst., Boston, MA, 02115
J Med Chem; 25(4):478-481 1982

The compounds 9,10-anhydrodaunorubicin and 9,10-anhydroadriamycin as well as 9,10-anhydro-N-(trifluoroacetyl)adriamycin 14-valerate (9,10-anhydro-AD 32), were prepared starting from daunorubicin, adriamycin, and N-(trifluoroacetyl)adriamycin 14-valerate, respectively. In addition, 9-deoxydaunorubicin and 9-deoxy-N-(trifluoroacetyl)adriamycin 14-valerate were obtained by catalytic hydrogenation of the appropriate olefin. All of the products were significantly less active than the parent drugs in inhibiting the growth of CCRF-CEM (human lymphoblastic leukemic) cells in culture. The results suggest the importance of the tertiary alcohol function, as found in the parent compounds at the anthracycline 9 position, in contributing to the expression of biological activity of these agents. (Author abstract) (16 Refs)

60. ANTHRACYCLINE ANTIBIOTICS - STRUCTURE AND ANTITUMOR ACTIVITY.

Oki T, Takeuchi T
Nagoya Biochemistry Lab., Pfizer Taito Co., Ltd., 5-Gochi, Taketoyo-cho, Chita-gun, Aichi 470-23, Japan
Yuki Gosei Kagaku Kyokai Shi; 40(1):2-19 1982

Fermentation and purifications of various anthracyclines (AC), structures of AC antibiotics produced by microorganisms, biosynthesis of anthracyclinones, biochemical activities of various AC, and the relationship between the biochemical activities and structure were reviewed. In vitro biochemical activity tests included (1) blocking effects on nucleic acid and protein synthesis and cultured cell proliferation of L1210 leukemia cells, (2) Ames test, (3) uniting and breaking DNA chains, (4) metabolic pathways using rat liver homogenate, (5) sensitivity to NADPH-P450 reductase and xanthine oxidase and production of radicals, and (6) absorption by cultured L1210 cells. In vivo biochemical activity tests included predicting toxicity and anti-tumorigenicity against experimental tumors, distribution in mouse tissues, and cardiotoxicity of the drug in hamsters and rabbits. The in vivo studies with hamsters and rabbits suggested that improvement of pharmacological effects and toxicity was possible with partial anthracycline structure modification. Second stage animal studies evaluating drug anticancer effects, and directed towards various types of cancers, were thought to be necessary. (48 Refs) (In JPN)

INTERFERON AND OTHER ANTIVIRALS

61. ACTIVATION OF NATURAL KILLER CELLS AND INDUCTION OF INTERFERON AFTER INJECTION OF MOUSE HEPATITIS VIRUS TYPE 3 IN MICE.

Schindler L, Engler H, Kirchner H
(c/o Kirchner) Inst. Virus Res., German Cancer Res. Inst., 6900 Heidelberg, W. Germany
Infect Immun; 35(3):869-873 1982

High levels of natural killer (NK) cell activity and high titers of interferon were observed in the peritoneal exudate of C57BL/6 mice 20 to 50 h after injection of mouse hepatitis virus Type 3 (MHV3) but not during the first 10 h after infection. C57BL/6 mice were susceptible to MHV3 infection and showed high titers of MHV3 in the peritoneal exudate 48 h after infection. A/J mice, in contrast, were resistant to the dose that killed 100% of the C57BL/6 mice (10 macrophage-infecting doses) and showed considerably lower virus titers than those shown by C57BL/6 mice. NK cell activity and interferon titers were significantly lower in the peritoneal exudate of A/J mice than in that of C57BL/6 mice. Serum interferon titers were also lower in A/J mice. Thus, our data show an inverse relationship between resistance and the levels of these two parameters. The data suggest that, in contrast to the situation observed with certain herpesviruses, interferon and NK cells may not be of overwhelming importance in the defense of mice against MNV3. (Author abstract) (14 Refs)

62. SYNERGISM IN THE ANTITUMOR EFFECTS OF TYPE I AND TYPE II INTERFERON IN MICE INOCULATED WITH LEUKEMIA L1210 CELLS.

De Clercq E, Zhang ZX, Huygen K
Rega Inst. for Medical Res., Minderbroedersstraat 10, B-3000 Leuven, Belgium
Cancer Lett; 15(3):223-228 1982

Combined murine interferon-beta (MuINF-b) and murine interferon-gamma (MuINF-g) therapy in the murine L1210 system was evaluated. BDF1 mice were used. The interferon preparations were injected ip at different doses. Treatment was started immediately after tumor cell inoculation and given once daily for 16 days. Control mice did not receive any treatment. All BDF1 mice that were inoculated with L1210 cells died within 13-26 days after tumor cell inoculation. Their mean survival time (MST) was 18.5 days. Following treatment with MuINF-g at 10(2) units/mouse (UM) the MST increased to 20.2 days, and following treatment with MuINF-b at 10(3) UM the MST increased to 23.2 days. Neither increase was statistically significant. MST was prolonged to 30.3 days when both treatment regimens were combined and the increase was highly significant. With MuINF-g at 10(3) UM a barely significant increase in MST to 23.7 days was noted. MST increased to 27.1 days if MuINF-g at 10(3) UM was combined with MuINF-b at 10(3) UM. At 10(4) UM MuINF-b increased the MST to 29.2 days. This increase was highly significant, and combination of MuINF-g at 10(4) UM with MuINF-b at 10(2) UM did not result in a further increase in MST (28.3 days). Combination of MuINF-b at 10(4) UM with MuINF-g at 10(3) UM did not substantially increase the MST (30.9 days) over that achieved by treatment with MuINF-b alone (29.2 days). (12 Refs)

63. COMPARATIVE EFFICACY OF ANTIHERPES DRUGS IN DIFFERENT CELL LINES.

De Clercq E
Rega Inst. Medical Res., Univ. Leuven, B-3000 Leuven, Belgium
Antimicrob Agents Chemother; 21(4):661-663 1982

A selection of antiherpes compounds including bromovinyldeoxyuridine (BVDU), acyclovir (ACV), and fluoroiodoaracytosine (FIAC) were compared for their inhibitory effects on herpes simplex virus type 1 (strain KOS) replication in a wide variety of human, simian, feline, and murine cell lines. The 50% inhibitory doses of the compounds varied considerably from one cell line to another, ie, from 0.01 to 2 ug/ml for ACV and from 0.004 to 0.2 ug/ml for BVDU and FIAC. However, the relative order of antiviral potency remained constant, thus (in order of decreasing potency) BVDU greater than FIAC greater than ACV, for all cell lines studied except for the murine embryo cells, in which the order of decreasing potency was BVDU greater than ACV greater than FIAC, and for the feline lung cells, in which the order of decreasing potency was FIAC greater than ACV greater than BVDU. (Author abstract) (10 Refs)

64. EFFECT OF MOUSE INTERFERON ON CELL TRANSFORMATION AND VIRUS PRODUCTION IN RAT CELLS EXOGENOUSLY INFECTED WITH MOLONEY MURINE SARCOMA AND LEUKEMIA VIRUSES.

Huleihel M, Aboud M
Microbiology and Immunology Unit, Faculty Health Sciences, Ben Gurion Univ. Negev, Beer Sheva, Israel
Int J Cancer; 29(4):471-476 1982

Foci of transformed cells, produced by MSV(124), appeared to result only from the primary infection, since this virus stock yielded a virus-nonproducing infection. On the other hand, the majority of foci scored in MSV/MLV-infected cultures, were generated by multiple secondary infections with the progenies of the primary infection. Mouse interferon (IF) was highly inhibitory for cell transformation by both virus stocks. However, this inhibition was apparent in MSV(124) infected cultures only if IF was added at least 12 hr before infection, whereas in MSV/MLV-infected cultures IF was highly effective even if added 24 hr after infection. The inhibition of focus formation by MSV(124) was irreversible after removal of IF, suggesting that IF inhibited an early step before provirus integration into the host genome. By contrast, in MSV/MLV-infected cultures focus formation was almost completely restored after recovery from the IF effect. Nevertheless, examination of virus production after IF removal proved that in MSV/MLV infection, too IF exerted an inhibitory effect before provirus integration. (Author abstract) (38 Refs)

65. INVOLVEMENT OF THE KIDNEY IN CATABOLISM OF HUMAN LEUKOCYTE INTERFERON.

Bino T, Edery H, Gertler A, Rosenberg H
Israel Inst. Biological Res., Ness Ziona, Israel
J Gen Virol; 59(part1):39-45 1982

The metabolic fate of human leukocyte interferon (HuIFN-alpha) was studied after intravenous injection into rats and cynomolgus monkeys. At various intervals the animals were sacrificed and the HuIFN-alpha content determined in serum and various tissues, HuIFN-alpha quickly disappeared from the circulation and was found mainly in the kidneys, in which levels were at least 7-to 10-fold higher than in the liver, spleen, lung, heart, brain, and muscles. No interferon was detected in urine. Subcellular fractionation of kidney revealed that the mitochondrial-lysosomal fraction (15,000 g) had a high HuIFN-alpha content. It was also found that HuIFN-alpha was rapidly inactivated by two types of proteinases found in the lysosomal fractions of rat, monkey and human kidneys, with an optimal pH of 3 to 4. The inactivation was partially inhibited by either pepstatin or leupeptin. Inactivation was totally prevented by a mixture of both inhibitors. Since it is known that interferon is scantily excreted in urine, our findings suggest that the kidney serves as a main site for its degradation. (Author abstract) (20 Refs)

66. REGULATION OF 2-5 A SYNTHETASE ACTIVITY AND ANTIVIRAL STATE IN INTERFERON TREATED CHICK CELLS.

Lab M, Thag M, Soteriadou K, Koehren F, Justesen J
Faculte' de Medicine, Laboratoire de Virologie et Groupe de Recherches de INSERM U74, rue Koeberle, 6700 Strasbourg, France
Biochem Biophys Res Commun; 105(2):412-418 1982

The activity of 2'-5'oligoadenylate synthetase (2-5 A synthetase) and the antiviral state (AVS) of chick embryo fibroblasts following interferon (IFN) treatment were investigated. 2-5 A synthetase increased during IFN treatment and rose to a maximun level in 5-6 hr, remaining at this level as long as IFN was present in the culture medium. The AVS, measured by the inhibition of Sindbis virus yield, exhibited similar kinetics. Following removal of IFN, both the 2-5 A synthetase activity and the AVS were maintained for 9-10 hr, after which the activity decayed. If cycloheximide was added to the culture immediately following removal of IFN, this decay was not observed; both activities remained at the 5-6 hr peak level. This effect suggests that the decrease of 2-5 A synthetase is controlled by an unstable regulatory protein. To test if this regulation is due to either degradation of 2-5 A synthetase or reversible activation, the cells were treated for 6 hr with IFN, the IFN removed for the next 24 hr, and cycloheximide then added at 30 hr. For both the 2-5 A synthetase and AVS, removal of IFN again lead to a decay; however, inhibition of protein synthesis by cycloheximide at 30 hr produced an increase in both activities to the same level as when IFN was removed at 6 hr. This further suggests that an unstable protein reversibly inactivates the enzyme activity. In the same experiments, removal of cycloheximide after 18 hr produced a 'superinduction', an increase in the 2-5 A synthetase activity and AVS. This may be explained by the accumulation of mRNA for 2-5 A synthetase during the period of cycloheximide treatment, this mRNA being transiently inactivated by factors which require protein synthesis. (17 Refs)

67. CYTOTOXIC EFFECT OF ALPHA-INTERFERONS OF DIFFERENT ORIGIN.

Pokidysheva LN, Gulevich NE, Lavrukhina LA
N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Vopr Virusol; (1):32-34 1982

Cytotoxic effects of human, swine, and bovine leukocytic interferons (IF) were studied in cultured human lymphoblastic cells (J-96 and Namalva cell lines). All three IF provided a 50-60% inhibition of lymphoblastic cells. IF did not affect the growth of normal embryonal fibroblasts. (5 Refs) (In RUS)

68. INHIBITION OF MURINE RAUSCHER LEUKEMIA AFTER COMBINED ADMINISTRATION OF NEURAMINIDASE AND INTERFERON.

Kobrinskii GD, Barinskii IF, Efimova IV, Eremian LK
Res. Inst. Immunology, Moscow, USSR
Biull Eksp Biol Med; 92(1):62-64 1982

Therapeutic efficacy of neuraminidase (NA) in combination with interferon (IF) was studied in BALB/c mice bearing Rauscher leukemia (RL). The animals were inoculated ip with RL virus-containing spleen cells treated with NA; 4 hr prior to the inoculation with virus, the mice received single injections of IF (1,500 units). Of 30 mice treated with NA + IF, 27 survived, compared with 11/30 after treatment with NA alone and 0/30 after treatment with IF alone. NA alone and IF alone increased the av lifespan of mice with RL (25.5 days and 26.2 days, respectively, compared with 17.4 days in nontreated controls). (9 Refs) (In RUS)

OTHER RELATED STUDIES

69. EFFECT OF CERULOPLASMIN ON HEMATOPOIETIC SYSTEMS DAMAGED BY IRRADIATION OR BY AN INJECTION OF CYCLOPHOSPHAMIDE.

Yamada M, Morisuye SI, Hoshino T, Shimizu M
Res. Lab., The Green Cross Corporation, 3-5, Miyakojima-Nakadori, Miyakojima-ku, Osaka 534, Japan
Curr Ther Res Clin Exp; 3(3,part2):435-445 1982

Effects of ceruloplasmin (CER) on murine bone marrow that had been damaged by a single dose of whole-body irradiation (100 or 600 rad) or by injection of cyclophosphamide (CY: 15, 50, or 150 mg/kg, iv) was investigated. The survival of test animals was determined and the amount of spontaneous regeneration of hematopoietic committed stem cells (CFU-C) in the irradiated mice was measured. Irradiated mice received 1 mg CER/kg/day for 7 days before and 30 days after irradiation, or immediately after irradiation for 30 days. Control animals received 1 mg/kg/day of human gamma globulin immediately after irradiation and for 30 days. In controls, 60% irradiated with 100 rad and 11% irradiated with 600 rad survived. All the mice given CER before and after 100 rad survived, and 93% of those given CER after irradiation survived. Of those irradiated with 600 rad, 28% given CER before and after and 22% given CER only after survived. CER injections, while not directly preventing damage to the CFU-C, accelerated regeneration of CFU-C; numbers returned to normal on day 6 after irradiation, increased to approx 2x normal by day 14, and gradually returned to normal thereafter. Pretreatment with CER significantly reduced the lethal effect of CY if CER was injected before as well as after CY injection. Thus, CER had some therapeutic effect on the damaged hematopoietic system and pretreatment and continued treatment with CER may allow for longer, uninterrupted radiotherapy or chemotherapy. (19 Refs)

70. INTERACTION BETWEEN HEPARIN AND ADRIAMYCIN IN MICE BEARING THE LEWIS LUNG CARCINOMA.

Colombo T, Delaini F, Ferrari R, Donati MB, Donelli MG, Poggi A
Istituto di Ricerche Farmacologiche, Mario Negri, Via Eritrea 62, 20157 Milan, Italy
Biomedicine; 34(3):124-128 1981

This investigation was prompted by the observation that adriamycin can interact with heparin in vitro and reduces its anticoagulant activity in ex vivo tests in humans. The possible interactions between these two drugs were studied in C57Bl/6J mice bearing the Lewis lung carcinoma (3LL). The anticoagulant activity of heparin was temporarily reduced by concomitant treatment with adriamycin, as indicated by both activated partial thromboplastin times and blood recalcification times. In contrast, no changes were found in the kinetics of adriamycin disappearance from blood and accumulation in tissues if mice had been pretreated with heparin. Moreover, the effect of adriamycin on tumor and metastasis growth was unchanged by the association with the anticoagulant. These data indicate that the short-lived interaction between adriamycin and heparin, which can be documented by coagulation tests, does not necessarily involve a modification in the anticancer activity of the anthracycline. (Author abstract) (12 Refs)

71. THYMIDYLATE SYNTHETASE - SUBSTRATE COMPLEX FORMATION.

Danenberg PV, Lockshin A
Dept. Biochemistry and Comprehensive Cancer Center, Univ. Southern California, Sch. Medicine, Los Angeles, CA, 90033
Mol Cell Biochem; 43(1):49-57 1982

The complexes that thymidylate synthetase (TSase) forms with various potent inhibitors have been intensively studied and thoroughly reviewed. Of particular significance is the covalent ternary complex of TSase-FdUMP-5,10-CH2H4PteGlu. FdUMP is the active metabolite of the widely used anti-cancer drug 5-fluorouracil. This complex is thought to be analogous to a steady-state intermediate of the normal enzyme reaction with the substrate dUMP. In this review, we examine the properties of TSase-dUMP complexes in order to determine if there is an experimental basis for drawing a close analogy between dUMP and FdUMP in their interaction with TSase, and also to evaluate data indicating a potential chemotherapeutic value for TSase-dUMP complexes formed in the presence of folate analogs. (Author abstract) (50 Refs)

72. MODIFICATION OF BENZO[A]PYRENE-INDUCED TRANSFORMATION OF C3H/10T1/2 CELLS BY PREGNENOLONE-16ALPHA-CARBONITRILE AND DEXAMETHASONE.

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Cancer Lett; 15(3):215-221 1982

The effect of microsomal enzyme inducers, pregnenolone-16alpha-carbonitrile (PCN) and dexamethasone (DEX), on benzo[a]pyrene (BP)-induced transformation of C3H/10T1/2 cells is described. Data for benz[a]anthracene (BA) cytotoxicity and transformation which was used as a control, are presented. PCN increased the toxicity of BP and also increased the BP-induced transformation in a dose-dependent manner. Max enhancement of transformation occurred at 58 uM PCN and was 250% of the BP alone treated culture. DEX caused a dose-dependent reduction in BP-induced cellular transformation. Max reduction (65%) was observed at 23 uM DEX. DEX pretreatment also reduced the cytotoxic effect of BP. DEX treatment alone was not cytotoxic. The simultaneous treatment with DEX did abolish the toxic effect of BP, while PCN did not statistically alter BP toxicity. Both PCN and DEX only slightly induced aryl hydrocarbon hydroxylase (AHH) activity in the cells after a 24-hr treatment. The induction was maximal at approx 0.23 uM for DEX and 2.3 uM for PCN. The induction was much lower than that observed for BA. The greatest difference in metabolism of BP by pretreated C3H/10T1/2 cells occurred at 8-12 hr after the addition of BP. By 24 hr the amount metabolized in control and pretreated cells is nearly equivalent. Results suggest that a correlation between the ability of PCN and DEX to induce AHH activity or BP metabolism to water soluble products and their ability to alter transformation is not entirely consistent. (20 Refs)

73. DNA REPAIR AND THE GENETIC EFFECTS OF THYMIDYLATE STRESS IN YEAST.

Kunz BA, Haynes RH
NIEHS, Lab. Moleculair Genetics, P.O. Box 12233, Research Triangle Park, NC, 27709
Mutat Res; 93(2):353-375 1982

Resistance of certain rad mutants of Saccharomyces cerevisiae strains to thymineless death induced by aminopterin + sulfonamide is described. Defects in excision (rad3) or RAD6-dependent repair (rad6, rad18) appear to decrease the lethality and recombinagenicity of antifolate treatment. The results suggest a mechanism to explain one type of acquired resistance to methotrexate in mammalian cells. (48 Refs)

74. EFFECT OF CYCLOPHOSPHAMIDE ON THE ALPHA-FETOPROTEIN LEVEL IN BLOOD SERA OF MICE BEARING HEPATOMA 22A AT DIFFERENT STAGES OF TUMOR DEVELOPMENT.

Romanov IuA, Plaksina TI
Dept. Biology, N. I. Pirogov Second Medical Inst., Moscow, USSR
Biull Eksp Biol Med; 92(1):60-62 1982

The relationship between efficacies of antineoplastic agents and periods of tumor development was studied in male C3HA mice bearing hepatoma 22A. Within different time periods after tumor transplantation, the animals were injected with cyclophosphamide (CP, 100-150 mg/kg, sc). The blood level of alpha-fetoprotein (AFP) was determined by double immunodiffusion assay. In nontreated mice, the AFP was first detected on day 8 after tumor transplantation. Level of the AFP showed a progressive increase and reached a max on day 14. A second increase in AFP level was observed on day 19. CP administration on day 6 of tumor development caused a 4x decrease in AFP level. CP administration on day 7 did not affect the AFP level, while CP administration on days 11 or 16 caused an increase in the level. The most pronounced inhibition of AFP level was observed after CP administration on day 4. (6 Refs) (In RUS)

75. THE FREQUENCY OF INTERSTRAND CROSS-LINKS IN DNA FOLLOWING REACTION OF CIS-DIAMMINEDICHLOROPLATINUM(II) WITH CELLS IN CULTURE OR DNA IN VITRO: STABILITY OF DNA CROSS-LINKS AND THEIR REPAIR.

Roberts JJ, Friedlos F
Dept. Molecular Pharmacology, Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks., England
Chem Biol Interact; 39(2):181-189 1982

DNA that had been reacted in vitro with cis-diamminedichloroplatinum(II) (cisplatin) had the same frequency of interstrand cross-linking (namely, approx 1 cross-link per 150 platinum reaction) as that found in the DNA isolated from cells in culture immediately after their treatment with cisplatin. Incubation of both the in vitro and in vivo platinum-reacted DNA in sodium citrate buffer for 24 hr at 37 C resulted in up to a five-fold increase in cross-link frequency. (Author abstract) (11 Refs)

76. EFFECT OF ADRENORECEPTOR BLOCKADE ON HEMORRHAGIC NECROSIS OF METH A SARCOMATA INDUCED BY ENDOTOXIN OR TUMOR NECROSIS SERUM.

Bloksma N, Hofhuis FM, Willer JM
Lab. Microbiology, Catharijnesingel 59, 3511 GG Utrecht, The Netherlands
Immunopharmacology; 4(2):163-171 1982

The effects of alpha- and beta-adrenoreceptor blockade on the induction of hemorrhagic necrosis in Meth A sarcoma by endotoxin (ET) and tumor necrosis serum (TNS) are reported. TNS and normal mouse serum (NMS) were prepared in approx 14 wk old female Swiss random bred mice (wt approx 30 g). Tumor experiments were performed with approx 12 wk old female BALB/c mice (wt approx 20 g). Mice with 9-day-old Meth A sarcomata received an ip injection with graded doses of phentolamine, propanolol, or saline followed by 25 ug ET. ET alone induced a significant reduction of the mean tumor size compared to the saline-treated controls. Two out of 5 mice had complete regression of their tumors. Neither dose of phentolamine, when given prior to ET, altered the mean tumor growth significantly. Propanolol did not substantially change the effects of ET on tumor growth, but the highest dose, 50 mg/kg potentiated the effect of ET. The effects of phenoxybenzamine (PBA) are presented. PBA given prior to ET reduced the antitumor effect of ET considerably. At day 14 the mean tumor size of animals treated with PBA and ET was in the range of the saline-treated controls, without any apparent relation to dose effect. PBA tends to induce a dose-dependent decrease of the extent of necrosis. Following an injection of saline or adrenoreceptor antagonist, tumor-bearing mice were injected iv with 0.2 or 0.5 ml TNS or NMS. A small quantity of TNS induced hemorrhagic necrosis in 3 out of 5 animals. pretreatment with phentolamine or PBA completely prevented the induction of hemorrhagic necrosis by 0.2 ml

TNS. No tumor regression was induced by TNS in the experiments. (16 Refs)

77. CHANGES IN PROSTAGLANDIN LEVELS IN CULTURES OF SV40-TRANSFORMED MACROPHAGE CELL LINES IN RELATION TO THEIR PHENOTYPIC EXPRESSION.

Tanigawa T, Suzuki T, Takayama H, Takagi A
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Microbiol Immunol; 26(1):59-66 1982

Prostaglandin (PRG) levels were determined in culture fluids of simian virus 40-transformed cells, line 28-12 and its subline, and the release of PRG by the cells when they are treated with lipopolysaccharide (LPS) and OK-432 (a streptococcal preparation from penicillin-attenuated Streptococcus pyogenes) was investigated. Low levels of PRG were detected in Dulbecco's modified Eagle's medium, and significantly higher levels (4,921 +-140 picog/ml) were detected in heat-inactivated fetal calf serum. 28-12 cells were cultivated for 16 days and the medium was changed every 4 days. A low level of PRG was detected in 4-day culture medium during the growing phase of the cells. When the proportion of phagocytic cells increased during the stationary phase, a decrease in PRG levels was observed. The levels of PRG remained lower than background levels and constant during the culture period when the 28-12 subline isolated by cultivation with cytosine arabinoside (28-12Ara) was cultivated without a change in the medium for 4 days. Non-phagocytic 28-12 cells and phagocytic 28-12Ara cells were cultivated for 24 hr in the presence and absence of LPS (1 ug/ml) and OK-432 (25 ug/ml). The release of PRG by 28-12Ara cells was markedly enhanced, whereas its release by 28-12 cells was not affected. The results indicate the correlation between the phenotypic change from the nonphagocytic to the phagocytic state and a decrease in PRG levels in culture fluids, and that phagocytic cells are responsive to PRG inducers, whereas nonphagocytic cells are not. (27 Refs)

78. ON THE DYNAMICS OF THE MICROFILAMENT SYSTEM IN HELA CELLS.

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Div. Biology, California Inst. Technology, Pasadena, CA, 91125
J Cell Biol; 93(1):122-128 1982

We measured the pools of unpolymerized and filamentous actin in homogenates of HeLa cells made in several different lysis buffers, as well as after treatment of cells with a variety of chemicals or trypsin, and after adenovirus (Type 2) infection. This was possible when a series of factors concerning the basic culture conditions were kept constant: eg, serum type used, serum batch, cell density, time after subcultivation of cells, and buffering substance in the medium. Homogenates from untreated cells usually contain 35-45% of the total actin in an unpolymerized form. With some batches of cells this number can be as high as 50%. In sparse cultures (3 x 10(4) cells/cm2), HeLa cells contain approx 10 pg actin/cell, while the corresponding number is only 5 pg in dense cultures (3 x 10(5) cells/cm2). Treatment of cells with cytochalasin B increases the pool of unpolymerized actin by approx 30-40%, while colchicine decreases the fraction of unpolymerized actin by 20%. The oxidant diamide increases the filamentous actin pool 25-50%. Glucose, sodium azide, dinitrophenol, serum starvation, or thymidine treatment does not affect the distribution between unpolymerized and filamentous actin to any significant extent. Trypsin and EDTA induced rounding up of cells but did not change the actin distribution. The distribution of actin between G- and F-forms was unchanged after adenovirus infection. These results show that significant changes in the actin pools can be induced in nucleated cells. However, several treatments which alter the morphology and motility of cells are not accompanied by an alteration in the G-/F-actin ratio. (Author abstract) (29 Refs)

79. ALLOGENEIC BONE MARROW TRANSPLANTATION FOR ACUTE LEUKEMIA REFRACTORY TO INDUCTION CHEMOTHERAPY.

Zander AR
Bone Marrow Transplantation Team, Univ. Texas M.D. Anderson Hosp., Houston, TX
Cancer Bull; 34(1):40-42 1982

Successful allogeneic bone marrow transplantation for primary refractory acute leukemia is described in a 20-yr-old white male. The effectiveness of total-body irradiation combined with an allogeneic bone marrow transplant is confirmed. Piperazinedione and fractionated total-body irradiation were used as cytoreductive treatment; good antileukemic efficacy compared to cytoxan and total-body irradiation was demonstrated. Low-dose methotrexate [15 mg/square meter (m2) on day 1; 10 mg/m2 on days 3, 7, and 11; weekly thereafter] was given as prophylaxis against graft-vs-host disease, which manifested itself 20 days after transplantation and again more definitely 16 mo after transplantation, with scleroderma-like involvement of the soft tissue of all extremities. Over the following 6 mo, a gradual response to immunosuppressive cyclophosphamide and prednisone was observed. (9 Refs)

80. ISOLATION AND PRELIMINARY CHARACTERIZATION OF A PHOSPHONOACETIC ACID-RESISTANT AND TEMPERATURE-SENSITIVE MUTANT OF HERPES SIMPLEX VIRUS TYPE I.

Daksis JI, Priemer MM, Chan VL
Dept. Microbiology and Parasitology, Univ. Toronto, Toronto, Ontario M5S 1A1, Canada
J Virol; 42(1):20-29 1982

A group of 43 phosphonoacetic acid (PAA)-resistant mutants of herpes simplex virus Type 1 was isolated after the mutagenesis of infected cells with nitrosoguanidine. One of these mutants, designated PAA1rts1, was found to be temperature sensitive (ts), that is, unable to replicate at 39.5 C, the nonpermissive temperature. Recombination analysis of PAA1rts1 indicated that the PAA1r mutation and the ts1 mutation are loosely linked and are located on two separate genes. PAA1rts1 showed a defect in viral DNA synthesis at 39.5 C, which presumably can be attributed to the production of a PAA-resistant and thermolabile DNA polymerase. PAA1rts1 was also defective in the shutoff of host DNA synthesis at the restrictive temperature. (Author abstract) (20 Refs)

81. MUTAGENICITY STUDIES WITH 2,4,5-T ON BACTERIA AND MAMMALIAN GERM CELLS.

Herbold BA, Machemer L, Rohrborn G
Inst. Toxicology, Bayer AG, Friedrich Ebert Strasse 217-219, D-5600 Wuppertal 1, W. Germany
Teratogenesis Carcinog Mutagen; 2(1):91-101 1982

The herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) was tested for mutagenicity in an Ames mutagenicity with microsomal activation, a dominant lethal test in rats, and a cytogenetic assay of Chinese hamster spermatogonia. The 2,4,5-T contained 0.05 ppm dioxin. Salmonella strains used were TA

98, 100, 1535, and 1537, with cyclophosphamide and trypaflavine as controls. 2,4,5-T was tested at 4-2,500 ug/plate. In the dominant lethal test rats were fed 0.1, 1, or 100 mg/kg 2,4,5-T for 8 wk and then mated. Corpora lutea, dead, and viable embryos were counted 12 days after mating, and the rate of dominant lethal mutations determined. For the cytogenetic assay male Chinese hamsters were fed 0, 0.5, 5, or 50 mg/kg 2,4,5-T per day for 5 days in one test, and 0 and 500 mg/kg on the same schedule in a second test. The 2,4,5-T was not mutagenic in any of these tests. These findings are compared with tests of 2,4,5-T in other systems. (46 Refs)

82. POTENTIAL OF INTENSE GAMMA-IRRADIATION OF HOST CELLS FOR ANALYSIS OF VIRUS-SPECIFIED TRANSCRIPTION AND REPLICATION.

Silver M, Dales S
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Can J Biochem; 60(3):279-283 1982

Intense gamma-irradiation from a cobalt source differentially affects macromolecular synthesis of cultured mammalian cells. Exposure of monkey BSC-1 or murine fibroblastic L2 cells to 40 or 70 krad (1 rad = 1 x 10(-2) J/kg) abolishes DNA and RNA synthesis almost entirely but reduces the formation of protein much less. A dose-response analysis of irradiation shows that synthesis of total RNA and the messenger component thereof, measured as the poly(A)-containing fraction, are equally diminished. Host cells in which formation of DNA and RNA are minimal can support normal or nearly normal replication and transcription rates of vesicular stomatitis and vaccina viruses. Therefore, use of pretreatment with gamma-irradiation, as employed here, should prove to be generally useful in examining virus-related transcription under circumstances in which application of drugs affecting gene expression, such as actinomycin D, is deemed undesirable. (Author abstract) (22 Refs)

83. CHROMOSOMAL LOCATION OF A HUMAN ALPHA INTERFERON GENE FAMILY.

Slate DL, D'Eustachio P, Pravtcheva D, Cunningham AC, Nagata S, Weissmann C, Ruddle FH
Cancer Metastasis Research Group, Pfizer Central Research, Groton, CT, 06340
J Exp Med; 155(4):1019-1024 1982

A series of human/rodent somatic cell hybrids were scored for the presence of DNA sequences hybridizing to an alpha-1 interferon DNA probe. Hybrids were generated by fusing Chinese hamster E36 cells with human BD melanoma cells, temperature-sensitive Chinese hamster ovary cells and human WBC, mouse A9 cells with GM17 human fibroblasts, or mouse A9 cells with GM589 human fibroblasts. Hybrids were karyotyped and tested for the presence of human marker isozymes. In human/Chinese hamster hybrid cells, sequences hybridizing to the human alpha1 interferon probe were clearly observed in cellular DNA when chromosome 9 was retained. In hybrids lacking chromosome 9, no human-specific bands were observed. Segregation of chromosome 9 below a frequency of 20-30% resulted in a failure to detect alpha1 interferon related sequences. With appropriate cell hybrids, it should be possible to map rodent alpha interferon-related DNA sequences. (25 Refs)

84. TETRAENE AND PENTAENE LEUKOTRIENES: SELECTIVE PRODUCTION FROM MURINE MASTOCYTOMA CELLS AFTER DIETARY MANIPULATION.

Murphy RC, Pickett WC, Culp BR, Lands WE
Dept. Pharmacology, Univ. Colorado Medical Sch., Denver, CO, 80262
Prostaglandins; 22(4):613-622 1981

A neoplastic mast cell tumor was grown in mice which had been raised since birth on a diet enriched with eicosapentaenoic acid. Intact harvested mastocytoma cells were stimulated with calcium ionophore A23187 to produce lipoxygenase products from the polyunsaturated fatty acids liberated from the cellular membranes. Leukotriene B4, B5, C4 and C5 were isolated and characterized by HPLC retention time, ultraviolet absorption spectrometry and mass spectrometry. The arachidonic acid content of the mast cell tumor lipids was altered from 9.2 to 3.9 mole % while eicosapentaenoic acid increased from 0.5 to 4.5 mole % in response to the fish oil-supplemented diet. The relative amounts of arachidonic and eicosapentaenoic acids (3.9 and 4.5 mole % respectively) were associated with similar amounts of LTB4 and LTB5 synthesized by the cells. These results suggest that the epoxide leukotriene (LTA) derivative can be made efficiently from either arachidonic or eicosapentaenoic acids when both are present in cellular lipids. In contrast, the ratio of LTC4 to LTC5 (10 to 1) indicates that the reaction of LTA with glutathione may be critically dependent upon the structure of the unsaturated fatty acid with the ratio of LTC4/LTB4 (2.0) more than 10x greater than that (0.16) for LTC5/LTB5. (Author abstract) (24 Refs)

85. INCREASED OR DECREASED IMMUNOGENICITY OF TUMOR-ASSOCIATED ANTIGEN ACCORDING TO THE AMOUNT OF VIRUS-ASSOCIATED ANTIGEN IN RAT TUMOR CELLS INFECTED WITH FRIEND VIRUS.

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Cancer Immunol Immunother; 12(2):119-123 1982

Grading of tumor-associated antigen (TAA) is described with particular reference to the amount of virus-associated antigen (VAA) newly produced by non-lytic virus infection. Complement-dependent cytotoxic sensitivity of Friend virus (FV)-KMT-17 rat fibrosarcoma cells to anti-VAA serum increased proportionally following serial passage generations with a max at passage 6. The absorbing capacity potentials for removing 50% of anti-VAA serum activity were 12.0x higher in FV-KMT-17 (F6), and 3.2x higher in FV-KMT-17 (F4) cells than in FV-KMT-17 (F2) cells. No difference in absorbing capacities of FV-KMT-17 (F0, 2, 4, and 6) for anti-TAA serum were observed. When WKA/Hok rats were immunized with FV-KMT-17 (F2, 4, 6 and 0) cells having various amounts of VAA and subsequently challenged with 10(5) or 10(6) viable KMT-17 cells, survival rates of 20.8%, 83.3%, 18.2% and 45.8%,respectively, were obtained. Immunization of FV-tolerant rats with FV-KMT-17 (F2, 4, and 6) cells resulted in similar levels of transplantation resistance without marked difference from the non-passage F0. Immunization of normal rats with a mixture of WLFT-6 rat thymoma cells [1.6 x 10(7) possessing an amount of VAA almost equivalent to that in FV-KMT-17 (F4)] and 5.0 x 10(7) KMT-17 cells resulted in lower transplantation resistance than for FV-KMT-17 (F4) cells alone, suggesting that VAA and TAA must be present on the same cell. The results indicated that TAA immunogenicity increases when an appropriate amount of VAA is expressed on the tumor cell surface and decreases when a relatively low or excessive amount of VAA is expressed. (22 Refs)

86. SOURCES AND BIOLOGY OF REGULATORY FACTORS ACTIVE ON MOUSE MYELOID LEUKEMIC CELLS.

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Cancer Res. Unit, Walter and Eliza Hall Inst. Medical Res., Royal Melbourne Hosp., Melbourne, 3050 Victoria, Australia
J Cell Physiol; Suppl1:175-183 1982

The cell types producing granulocyte-colony stimulating factor (G-CSF), the half-life of G-CSF in the serum, and the effects of endotoxin in modifying serum G-CSF levels were studied. Mice used were 3-mo-old male and female mice of the strains C57BL and BALB/c. Following a single iv injection of 5 ug endotoxin, the capacity of the serum to induce differentiation colonies of WEHI-3B cells rises rapidly to a peak at 3-6 hr. Groups of C57BL mice were injected iv with 5 ug endotoxin 4x/wk. Good responses were obtained following the first three injections but thereafter successive responses were weaker and after the seventh injection no significant rises in activity were observed. Irradiation (150-1,200 rad) did not prevent the mice from responding to a subsequent injection immediately after irradiation. Groups of BALB/c nu/nu (congenitally athymic) mice were injected with the same agent. Nu/nu mice exhibited a normal response to the injection and exhibited obvious elevations in serum differentiating activity. Effects of cocultivation of WEHI-3B cells with normal cells were studied. Neither normal BALB/c thymus nor peritoneal cells formed colonies in the type of agar medium used. Addition of thymus cells did not induce differentiation in WEHI-3B colonies. Addition of 10(6) BALB/c peritoneal cells caused a marked differentiation of WEHI-3B colonies. Serum differentiating activity half-life varied between 1.5 and 2.3 hr. Groups of BALB/c mice were sc injected with 10(6) WEHI-3B cells. Recipient mice developed sc tumors within 3-4 wk of transplantation. No elevated levels of differentiating activity were observed. (41 Refs)

87. ACTIVATION OF NON-EXPRESSED BOVINE PAPILLOMA VIRUS GENOMES BY TUMOUR PROMOTERS.

Amtmann E, Sauer G
Inst. Virus Res., German Cancer Res. Center, 6099 Heidelberg, W. Germany
Nature; 296(5858):675-677 1982

Following infection of mouse embryo fibroblasts (MEF), bovine papilloma virus type 1 (BPV-1) genome resides in a non-expressed episomal state. After passaging of the BPV-1 infected cells, the viral DNA is eventually lost due to failure to replicate, as shown by hybridization of the viral DNA to a BPV-1 DNA probe according to the Southern method. When BPV-1-infected MEF cells were treated with the tumor promotor 12-O-tetradecanoylphorbol-13-acetate (TPA), considerably more BPV-1 DNA was found after 4 days than in the non-treated cells. Even when TPA was administered to cells in the passage 3 after infection, viral DNA could be detected while none was detectable in non-treated passage 3 cells. Viral DNA was detected at passages 1 and 5 after TPA removal, indicating that BPV-1 DNA continues to replicate in the absence of TPA. TPA also promoted viral transcription. While no viral RNA sequences could be detected in untreated MEF cells one passage after infection, 4 days after TPA treatment of a parallel culture, several species of BPV-1 RNA were found. The same RNA species were detected in BPV-1-induced hamster embryo fibroblasts. Similar results to TPA were obtained with 12-O-retinoylphorbol-13-acetate (RPA). In addition to induction of viral transcripts, TPA induced a transformed phenotype, expressed by an increase in saturation density of the cultures and the ability to grow in low serum medium. While several primate cell lines showed none of these effects, bovine fetal thyroid (BFT) cells did exhibit an enhanced DNA replication and a transient transcription and phenotypic transformation in the presence of TPA and RPA. Tumor promoter-treated MEF and BFT cells may provide a system for studying the amplification and expression of foreign genes inserted into a BPV-1 vector as well as a screening system for putative tumor-promoting agents. (22 Refs)

88. NECESSITY OF PROTECTIVE MEASURES IN CONNECTION WITH THE ADMINISTRATION OF INJECTABLE CYTOSTATICS.

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Tidsskr Nor Laegeforen; 102(3):180-181 1982

Safety measures recommended and implemented for the hospital personnel in connection with the administration of probably or positively carcinogenic and/or mutagenic cytostatics (cyclophosphamide, daunorubicin, doxorubicin, methotrexate, vinblastine and vincristine) are described. The safety measures include the use of special protective clothing and gloves and safe disposal of contaminanted materials. (17 Refs) (In NOR)

89. TUMOUR-PROMOTING DITERPENE ESTERS PREVENT MACROPHAGE ACTIVATION.

Keller R, Keist R, Hecker E

Immunobiology Res. Group, Inst. Immunology and Virology, Univ. Zurich, 8032 Zurich, Switzerland

Br J Cancer; 45(1):144-146 1982

Peritoneal wash-outs from normal DA rats or C3H/J mice were interacted for 8 hr with macrophage-activating lymphokines. 14C-Deoxythymidine-labeled DA rat polyoma-induced tumor cells were interacted with effector cells for 36 hr at 37 C; the released radioactivity was measured and net cytotoxicity calculated. The phorbol esters 12-O-tetradecanoyl-phorbol-13-acetate (TPA), phorbol-12,13-didecanoate (PDD), and the 1alpha-alkyldaphnane, Pimelea factor P2, were similarly active in preventing lymphokine-induced or spontaneous enhancement of macrophage tumoricidal activity. Manifestation of macrophage cytotoxicity was inhibited whether or not effector cells were first pretreated for 4 hr with tumor promoters and the washed effector cells interacted with prelabeled targets, or the promoting agents were present throughout the entire 36-hr effector/target cell interaction. Thus, active tumor promoters of the phorbol diester- and daphnane-type prevent lymphokine-induced enhancement of macrophage cytolysis; such a capacity to suppress activation or manifestation of cytotoxicity by rat and mouse macrophages may be common to all tumor promoters. Tumor promoters may facilitate the outgrowth of transformed cells by stimulation of their multiplication and functional capacities and by suppression of the host's cellular antitumor effector systems. (11 Refs)

90. THE PENETRATION OF MISONIDAZOLE INTO MATURE STRUCTURAL CARTILAGE.

Langler AJ, Bugden RD, Gibson P
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Br J Cancer; 45(2):282-285 1982

Mature cartilage may be expected to contain populations of hypoxic cells as a result of the tissues' lack of direct vascularization and structure; it may therefore be at risk from possible radiosensitization. The hypoxic-cell radiosensitizing drug misonidazole RO-07-0582 (MISO) was administered iv to mature New Zealand White rabbits at a dose of 100 mg/kg, and the resulting drug concentrations in both blood and ear-cartilage samples measured by HPLC. Samples were taken at regular intervals up to 4 h after administration of MISO. Blood concentrations of MISO rose rapidly to 240 ug/ml within 5 min of administration, before falling steadily, with a t1/2 of 45 min. Cartilage levels reached a peak of 70% of the blood levels approx 30 min after administration. The levels of MISO then fell, with a t1/2 of 44 min. (Author abstract) (24 Refs)

91. SYNERGISM OF CHLORPROMAZINE AND HYPERTHERMIA IN TWO MOUSE SOLID TUMOURS.

George KC, Singh BB
Biology and Agriculture Div., Bhabha Atomic Res. Centre, Trombay, Bombay 400 085, India
Br J Cancer; 45(2):309-313 1982

The effect of chlorpromazine HCl (CPZ) on the thermal sensitivity of sarcoma 180 (S180) and mouse fibrosarcoma (MFIB) was investigated. Both tumors were serially transplantable and grown sc on the ventral wall of the thorax of 8-wk-old female Swiss mice. When the tumors reached a mean diameter of 7-8 mm, the animals were treated with CPZ alone (5 mg/kg body wt), heat alone (up to 42.5 C), or both CPZ and heat. CPZ was administered as a single injection directly into the center of the tumors in unanesthetized mice 5 min before heating; heat treatment was given for 1 hr after the max temperature was attained. Neither treatment with CPZ alone nor heat alone to 40.5 C influenced growth of S180. Tumors completely regressed with heating alone to 41.5 or 42.5 C. Little CPZ effect was observed in S180 tumors. With MFIB, neither the drug alone nor the heat treatment alone at 41 C, nor any combination of the two affected tumor growth. However, administration of CPZ prior to heating to 42 C substantially delayed tumor growth compared with tumors heated without CPZ. No cures were observed. The different responses of the two tumors to combined treatment with CPZ and heat were attributed to differences in the membrane fluidity of the tumors; the S180 membrane is relatively more fluid than that of MFIB. Use of CPZ as a hypoxic cell radiosensitizer is suggested. (23 Refs)

92. 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) INDUCES SISTER-CHROMATID EXCHANGES AND DELAYS IN CELL PROGRESSION IN CHINESE HAMSTER OVARY AND HUMAN CELL LINES.

Schwartz JL, Banda MJ, Wolff S
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Mutat Res; 92(1/2):393-409 1982

In Chinese hamster ovary (CHO) cells and SV40-transformed human fibroblast cell lines (GM637 and XP12RO), 12-O-tetradecanoylphorbol-13-acetate (TPA: 1.0 nanog-1.0 ug/ml) caused a 20-45% increase in the frequency of sister chromatid exchanges (SCEs). This increase in SCEs was not caused by an impurity in the TPA preparation, or increased 5-bromo-2'-deoxyuridine uptake into DNA; it was independent of the incubation time between TPA exposure and fixation of the cells. Simultaneous exposure to TPA (1.0 ug/ml) and benzo(a)pyrene (BP: 1.7 x 10(-5)-3.3 x 10(-6) M) led to a synergistic SCE induction in CHO cells. No synergism was observed after simultaneous exposure to TPA (1 ug/ml) and mitomycin C (0.03 ug/ml) or UV light. In addition to its weak SCE-inducing effects in CHO cells, TPA alone caused a slight delay in cell cycle progression and markedly enhanced the cell cycle delay induced by BP. The SCE-inducing capacity of TPA in these cells was unrelated to its toxicity, because TPA was not toxic at the doses used. It also seemed to be unrelated to excision repair capacity, because TPA caused similar increases in SCE frequency in cells which were proficient (GM637), mildly deficient (CHO), and severely deficient (XP12RO) in excision repair. The significance of SCE induction and its relationship to other biologic effects of TPA remain unknown. (40 Refs)

93. THE IDENTITY OF INTERFERON-BETA1 MRNA TRANSCRIPTS IN HUMAN FIBROBLASTS AND NAMALVA CELLS.

Gross G, Bruns W, Mayr W, Collins J
Abt. Genetik, Gesellschaft fur Biotechnologische Forschung mbH, Mascheroder Weg, 3300 Braunschweig, W. Germany
FEBS Lett; 139(2):201-204 1982

The messenger RNA (mRNA) for interferon-beta1 (IFN-b1) induced in different cell types by different modes of induction were compared. Synthesis of mRNA for IFN-b1 production was induced in human fibroblast cultures by exposure to cycloheximide (50 ug/ml) and polyriboinosinic-polyribocytidylic acid (50 ug/ml). Synthesis of mRNA for IFN-b1 was induced in lymphoblastoid Namalva cells by exposure to Sendai virus for 5 hr. The DNA fragment EcoRI-F, which contains the entire IFN-b1 gene was used for S1 mapping. Klenow polymerase was used for 3'-end labeling. T4 DNA kinase was used for 5'-end labeling. Denaturing on 2% agarose gel indicated that IFN-b1 produced by the human fibroblasts was the same size as IFN-b1 produced by Namalva cells. Mapping studies indicated that mRNA for IFN-b1 induced by either system was 840 nucleotides in length without the poly(A) tail. The 5'-end labeled BglII fragment gave rise to a 640 nucleotide fragment; the 3'-end labeled fragment BglII fragment gave rise to a 200 base-pair fragment that was protected against S1-digestion. Results indicate that mRNA for IFN-b1 induced in different cell types by different induction systems can be of identical size. (15 Refs)

94. 12-O-TETRADECANOYL-PHORBOL-13-ACETATE AND ITS RELATIONSHIP TO SCE INDUCTION IN SYRIAN AND CHINESE HAMSTER CELLS.

Popescu NC, Amsbaugh SC, Larramendy ML, DiPaolo JA
Lab. Biology, Building 37, Room 2A19, NCI, Bethesda, MD, 20205
Environ Mutagen; 4(1):73-81 1982

Alteration of cell culture conditions, 12-O-tetradecanoylphorbol-13-acetate (TPA), or 5-bromodeoxyuridine (Burd) concentrations, or temporal relation between UV or x-irradiation and TPA had no effect on sister chromatid exchange (SCE) induction of Syrian hamster embryo cells (HEC). SCE frequencies were determined on exponentially growing and stationary HEC cultures incubated with different Burd concentrations for one or two replicative cycles. TPA (0.01-2.0 ug/ml medium) was ineffective in inducing SCE in HEC cultures cultivated in medium supplemented with heat-inactivated serum, independent of Burd concentration (1.0-10.0 ug/ml) and the number of cell divisions post treatment. In a similar study, TPA did not increase SCE frequency in V79-4 Chinese hamster cells in heat-inactivated or noninactivated serum. TPA has no effect on UV or x-irradiation induced SCE. X-irradiation (200 R) causes an increase of only 1 SCE/cell over the control value, while UV (1.5 and 3.0 J/square meter) causes an increase of 10 and 24 SCE per metaphase. TPA addition either immediately or 48 hr after UV or x-irradiation did not alter SCE frequency obtained by irradiation alone. Although SCE induction may be important for the induction of transformation by environmental agents, the enhancement of transformation frequency caused by TPA occurs without further DNA alterations involved in SCE formation. (21 Refs)

95. FACTORS DETERMINING THE EFFECTIVENESS OF HYPOXIC CELL RADIOSENSITIZERS.

Vynskaya NP, Vygodskaya AL, Zharkov SA, Yarmonenko SP
All-Union Oncologic Scientific Center, Moscow M-478, USSR
Stud Biophys; 86(1):49-50 1981

Data on the relationship between irradiation conditions (acute or prolonged hypoxia) and the radiomodifying effectiveness of metronidazole (MNZ) are presented. MNZ was injected at the beginning of prolonged (20 min) or 20 min before acute (1 min) hypoxia in mice. A considerable radiosensitizing effect was observed at acute hypoxia. The absence of radiosensitizing effect in prolonged hypoxia could be explained by the increase in PO2 in critical systems such as stem cell populations caused by adaptation to hypoxic conditions and/or the MNZ injection which affected drug absorption and metabolism. Evidence supporting the former explanation is presented. (5 Refs)

96. MECHANISM OF ACTION OF RADIOSENSITIZING COMPOUNDS WITH SIMILAR ELECTRON AFFINITY.

Gazso L
Orszagos 'Frederic Joliot-Curie' Sugarbiologiai', Sugaregeszsegugyi Kutato Intezet, Budapest, Hungary
Magy Onkol; 26(1):36-44 1982

Radiosensitizing compounds with similar electron activity and their possible mechanism of action are reviewed. 5-Nitro and 2-nitro-substituted nitroimidazole derivatives (metronidazole, 2-nitroimidazole and misonidazole) are the most promising radiosensitizing compounds with similar electron activity. Their action is probably based on an increase in the number of free radicals due to electron capture. (37 Refs) (In HUN)

97. INHIBITION OF DNA SYNTHESIS ACCOMPANIED BY STIMULATION OF PROTEIN SYNTHESIS IN NOVOBIOCIN-TREATED DEVELOPING SEA URCHINS.

Speck WT, Rosenkranz PG, Rosenkranz HS
Dept. Pediatrics, Sch. Medicine, Case Western Reserve, Cleveland, OH, 44106
Mutat Res; 104(1-3):125-130 1982

The effects of novobiocin (NB) on DNA synthesis and protein synthesis were studied in developing American sea urchins, Arbacia punctulata. Gametes of the sea urchin were obtained by electric stimulation and exposed to NB in sea water 10 min after fertilization. Development was examined at intervals. In metabolic studies embryos were exposed to [3H]lysine, [3H]thymidine, or [3H]cytidine after exposure to NB. NB produced developmental abnormalities in a dose-dependent manner. At the highest level tested (1,000 ug NB/ml) embryotoxic effects were characterized by early developmental arrest and abnormal cleavage patterns. At concentrations of 100 or 330 ug NB/ml development was arrested in the blastula stage. At 100 ug/ml blastulae remained viable for 2 days or longer. At concentrations of 10 or 33 ug/ml developmental retardation began in the gastrula stage. At 33 ug ml development was arrested in the pluteus stage. At 10 ug/ml development eventually caught up with growth in controls. Concentrations of 3.3 ug/ml produced no apparent effects on development. DNA synthesis was inhibited by increasing levels of NB. RNA synthesis was inhibited at low levels, but inhibition decreased as NB levels increased. Protein synthesis was stimulated by increasing levels of NB. Hydroxyurea (HU) inhibited DNA synthesis but did not stimulate protein synthesis, indicating that NB and HU act on different enzyme subunits. (17 Refs)

98. EMBRYOTOXICITY OF 3,3',4,4'-TETRACHLOROAZOBENZENE AND 3,3',4,4'-TETRACHLOROAZOXYBENZENE IN THE CHICK EMBRYO.

Schrankel KR, Kreamer BL, Hsia MT
(c/o Hsia) 237 Russell Laboratories, Univ. Wisconsin, 1630 Linden Drive, Madison, WI, 53706
Arch Environ Contam Toxicol; 11(2):195-202 1982

The chick embryo assay was run on F1(NH x SCWL) chicken eggs given a single air cell injection of 0.0001-100 ug of 3,3',4,4'-tetrachloroazobenzene (TCAB) or 0.0005-100 ug of 3,3',4,4'-tetrachloroazoxybenzene (TCAOB) on days 4 (all doses) or 11-13 (only 0.05 ug) of incubation. LD50 for TCAB was 44 ng, and for TCAOB, 12 ng. The incidence of severe, non-dose related sc edema from 0.01-1.0 ug of TCAB was 2.5-5.1%, and from 0.005-0.05 of TCAOB was 2.1-22.5%. Other malformations included altered feather pattern and lack of down, hemorrhage, external viscera, reduced body size, failure to withdraw the yolk sac, beak malformation, dilation of blood vessels, and monomicropthalmia. (38 Refs)

99. STUDIES ON THE MECHANISM OF NK CELL LYSIS.

Quan PC, Ishizaka T, Bloom BR
Dept. Microbiology and Immunology, Albert Einstein Coll. Medicine, Bronx, NY
J Immunol; 128(4):1786-1791 1982

The mechanism of cytolysis by murine NK cells was analyzed using a variety of metabolic inhibitors that have proven informative in studying the lytic mechanism of CTL and the mechanism of histamine release by mast cells. Target cell binding occurred in the absence of calcium and was inhibited by only one of the agents studied, cytochalasin B. Lysis was initiated by addition of Ca++ ions, as in the case of CTL. Subsequent to target cell binding, but prior to programming for lysis by Ca++, NK cell lytic activity could be suppressed by inhibitors of chymotrypsin-like, but not trypsin-like proteases, in contrast to CTL. In addition, 3-deaza-SIBA, an inhibitor of transmethylation reactions and quinacrine, an inhibitor of phospholipase A2, appear to act before the Ca++-dependent programming for lysis. Sr++ ions blocked the lytic function, as did trifluoperazine (stelazine), the former presumably competing for ionic calcium, the latter known to block binding of Ca++ to calmodulin. 8Br-cAMP and colchicine blocked later steps required for lysis. With the possible exception of trifluoperazine, all of the agents that blocked NK cell lysis are known to inhibit histamine release from mast cells. These results lend support to the stimulus-secretion model, originally proposed to explain the mechanism of CTL cytolysis, as relevant to the mechanism of lysis by NK cells. (Author abstract) (38 Refs)

100. GLUCOCORTICOIDS DOWN-REGULATE SOMATOSTATIN RECEPTORS ON PITUITARY CELLS IN CULTURE.

Schonbrunn A
Lab. Toxicology, Dept. Physiology, Harvard Sch. Public Health, Boston, MA, 02115
Endocrinology; 110(4):1147-1154 1982

Treatment of GH4C1 cells, a clonal strain of rat pituitary tumor cells which synthesize and secrete PRL and GH, with 5 x 10(-6) M cortisol caused a time-dependent decrease in [125I-Tyr1]SRIF-specific binding. Receptor affinity was the same in control and cortisol-pretreated cells, but the number of SRIF-binding sites decreased from 21,900 to 15,200 receptors/cell. Pretreatment of cells with 5 x 10(-7) M dexamethasone (1,4-pregnadien-9-fluoro-16alpha-methyl 11beta,17alpha,21-triol-3,20-dione) for 43 hr caused the same maximal decrease in [125I-Tyr1] somatostatin (SRIF)-specific binding as 5 x 10(-6) M cortisol; however, dexamethasone was 10x more potent than cortisol. Pretreatment of GH4C1 cells for 43 hr with 5 x 10(-6) M 17beta-estradiol, 17alpha-methyltestosterone, testosterone, or progesterone had no effect on [125I-Tyr1]SRIF-specific binding, indicating that this effect was glucocorticoid specific. Treatment of GH4C1 cells with both dexamethasone and cycloheximide caused the same decrease in [125I-Tyr1]SRIF-specific binding as did either agent alone. In contrast, the down-modulation of SRIF receptors by chronic TRH treatment was previously shown to be additive with cycloheximide. However, maximal concentrations of TRH and cortisol added together had no greater effect on SRIF receptors than TRH alone. Therefore, even though the effects of TRH and cortisol are differentially sensitive to cycloheximide, the pathways by which they down-regulate SRIF receptors probably overlap at a common rate-limiting step. In conclusion, the receptors for TRH and SRIF are modulated in opposite directions on GH4C1 cells by chronic glucocorticoid treatment. Since these two hypothalamic peptides have opposing effects on hormone release, such receptor modulation may play an important role in regulating pituitary responsiveness to these hypothalamic regulatory factors. (45 Refs)

101. GLUTAMINE SYNTHETASE INDUCTION BY GLUCOCORTICOIDS IN THE GLUCOCORTICOID-SENSITIVE HUMAN LEUKEMIC CELL LINE CEM-C7.

Harmon JM, Thompson EB
Div. Cancer Biology and Diagnosis, Lab. Biochemistry, NIH, NCI, Bethesda, MD, 20205
J Cell Physiol; 110(2):155-160 1982

Glucocorticoid stimulation of glutamine synthetase (GS) was studied in the glucocorticoid-sensitive human leukemia cell line CEM-C7. When cells were grown in the presence of 10(-6) M dexamethasone (DEX) for various time periods and then assayed for GS activity, after a lag of 1-2 hr, enzyme activity increased 2.0-2.5-fold to a value of approx 4.5 x 10(-2) micromoles/min/mg. This effect was max after 12 hr of DEX treatment. The relationship of GS activity to steroid concentration was determined by incubating cells with various concentrations of DEX for 18 hr. Half-max GS response was obtained with 2 x 10(-8) M and max response with 2 x 10(-7) M DEX. Direct proof that GS elevation is a receptor-mediated phenomenon was obtained by examining the response of GS induction in a subclone of CEM-C7 (ICR-27) that contains no glucocorticoid receptor. At concentrations of 2 x 10(-7) M, DEX elicited maximal GS response, whereas prednisolone and cortisol, less potent glucocorticoids, elicited correspondingly lower responses. The inactive glucocorticoid cortexolone and the nonglucocorticoids progesterone, 17-beta-estradiol, and 5-alpha-dihydrotestosterone produced no elevation in GA activity demonstrating that GS induction in CEM-C7 cells is a glucocorticoid-specific response. GS synthesis required RNA and protein synthesis and the continued presence of of a glucocorticoid. Increased GS activity induced by DEX did not appear to result from glutamine deprivation. In contrast to its antagonism of GS induction, bromodeoxyuridine did not interfere with the ability of DEX to inhibit growth in CEM-C7 cells. (34 Refs)

102. REGULATION OF DIHYDROFOLATE REDUCTASE GENE TRANSCRIPTION IN METHOTREXATE-RESISTANT MOUSE FIBROBLASTS.

Wu JS, Johnson LF
(c/o Johnson) Dept. Biochemistry, Ohio State Univ., Columbus, OH, 43210
J Cell Physiol; 110(2):183-189 1982

DNA-excess filter hybridization was used to study the rate of synthesis of dihydrofolate reductase (DHFR) heterogeneous nuclear (hn)RNA in serum-stimulated M50L3 cells, a methotrexate-resistant mouse 3T6 cell line. The rate of synthesis of DHFR hnRNA relative to total hnRNA varied over a considerable range when resting M50L3 cells were induced to reenter the cell cycle. The percentage of total hnRNA synthesized during a 20-min labeling period that hybridized to DHFR complementary (c)DNA was about 0.02-0.03% in resting M50L3 cells. When resting cells were serum stimulated to reenter the cell cycle, the percentage decreased initially to approx 0.01%, then began increasing about 6 hr following stimulation, and reached a max of approx 0.08% by approx 15 hr after stimulation. The relative rate of DHFR hnRNA synthesis began increasing at approx the same time (6 hr) and increased to approx the same extent by 15 hr following stimulation (3-4-fold) as does the relative rate of cytoplasmic DHFR mRNA. It was suggested that changes in the relative rate are primarily due to changes in the transcription of the DHFR gene. However, it is possible that the rate of synthesis of DHFR hnRNA remains relatively constant but that changes in the rate of synthesis of total hnRNA are responsible for alterations in the relative rate of DHFR hnRNA synthesis. The intracellular signals responsible for controlling DHFR gene expression are not known. High intracellular cyclic AMP was able to suppress DHFR gene transcription even when progression through the cell cycle was not blocked. The relationship of DHFR gene transcription to entry into the S phase was examined. (19 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

ANTITUMOR AGENT EFFICACY IN VIVO

1. THE TUMOR GROWTH REGRESSIVE EFFECT OF THREE TYPES OF ANTITUMOR DRUG ON HUMAN PROSTATIC CARCINOMA TRANSPLANTED IN NUDE MICE, AND THEIR IN VIVO MOVEMENT.

Akimoto M, Tsuboi N, Kawamura N, Nakajima H, Yui Y, Yoshida K, Nishimura T, Kawai H

Dept. Urology, Nippon Medical Sch., Japan

Hinyokika Kiyo; 27(12):1497-1504 1981

The growth regressive effect of NK631, mitomycin C and 5-Fluorouracil on human prostatic carcinoma transplanted in nude mice, and their distribution in the tumor, kidney, and skin and sc tissue were examined. The results were as follows: (1) NK631 showed the growth regressive effect in 15 mg/kg (2 x/w, ip) administered group and distributed in the kidney, tumor and skin and sc tissue in high concentration. (2) MMC showed the growth regressive effect in 2 mg/kg (1 x/w, ip) administered group and distributed in the kidney and tumor in high concentration and in the skin and sc tissue in low concentration. (3) 5-FU showed the growth regressive effect in 30 mg/kg (2 x/w,ip) administered group and distributed in the kidney and tumor in high concentration and in the skin and sc tissue in moderate concentration. (4) In therapeutic experiments of anticancer drug on human tumor transplanted in nude mice, care must be taken at the judgement of the growth regressive effect of the drug which distributes in the skin and sc tissue in high concentration whenever the tumor was transplanted in sc tissue. (Author abstract) (12 Refs) (In JPN)

2. EXPERIMENTAL STUDIES ON REGIONAL THERAPY OF URINARY BLADDER CANCER. 2. INSTILLATION OF MITOMYCIN C INTO RABBIT BLADDER.

Nemoto R, Iwata K, Mori H, Abe R, Kato T, Harada M

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Nippon Hinyokika Gakkai Zasshi; 72(9):1120-1128 1981

Instillation of ferromagnetic mitomycin C microcapsules (FM-MMCmc) was studied in male Japanese white rabbits bearing transplanted V2 carcinomas of the urinary bladder. The FM-MMCmc (307 +-34.5 micrometer diameter granules) were instilled via cystostomy 3 days after transplantation of the V2 carcinoma. The FM-MMCmc were guided to the tumor surface by an external magnet, and the tumor size was measured 2 wk after treatment. The 50% and 90% inhibitory doses of the mitomycin C (MMC) on the V2 carcinoma were approx 0.5 ug and 1 ug, respectively; this was similar to the sensitivity of the T24 MGH-UI human cultured bladder carcinoma. Compared to control rabbits and rabbits administered non-encapsulated MMC, tumor growth rates of the rabbits treated with FM-MMCmc were significantly lower, suggesting that intravesical instillation of FM-MMCmc with magnetic control was an effective therapy for V2 bladder cancer. MMC levels in the bladder wall, peripheral blood, and urine of the FM-MMCmc rabbits were higher than those in the non-encapsulated MMC rabbits. Use of magnetically controlled FM-MMCmc was thought to have potential as a new method of intravesicular treatment for bladder cancer as it released higher sustained concentrations of the drug in a selected area. (11 Refs) (In JPN)

3. PHASE-SPECIFIC CYTOTOXICITY IN VIVO OF HYDROXYUREA ON MURINE FIBROSARCOMA PULMONARY NODULES.

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Br J Cancer; 45(3):438-446 1982

The cytotoxic effects in vivo of hydroxyurea (HU) on murine fibrosarcoma (FSa) cells grown as pulmonary tumors were determined. Tumor cells from 13-day-old nodules were made into suspension and separated on the basis of cell size by centrifugal elutriation. Flow microfluorometry (FMF) was used to determine the cell-cycle parameters and the relative synchrony of the separated populations, as well as the degree of contamination by normal diploid cells in each of the tumor-cell populations. HU cytotoxicity was tested by administering both a single 1 mg/g ip dose into mice that had been injected iv 20 min earlier with known numbers of synchronized viable FSa cells, and ip doses of 1 mg/g each into mice bearing 13-day-old pulmonary nodules. In the latter experiments, animals were killed 1 h after the last dose, and the tumor nodules were excised and made into a single-cell suspension and elutriated. Known numbers of cells from each fraction were injected into recipient mice to determine survival. In both sets of experiments, cell killing by HU correlated with the percentage of S-phase cells. The treatment of 13-day-old pulmonary nodules with three doses of HU also depleted the (G2 + M) phase tumor cells and increased the heterogeneity between tumor subpopulations, as determined by FMF analysis. (Author abstract) (18 Refs)

4. INCREASED SURVIVAL DUE TO RADIOACTIVE ESTRADIOL IN MICE WITH C3HBA OR BW 10232 TUMORS.

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Cancer Chemother Pharmacol; 8(1):23-26 1982

The effect of graded doses of labeled and unlabeled estradiol (ED), when given in doses comparable to those used in physiologic and pharmacologic experiments, on C3HBA or BW 10232 tumor growth (TG) was studied in female C3H/HeJ and C57BL/6J mice. The effects of 1-5 uCi tritiated ED on TG and host survival in the C3HBA model are presented. Treatment for 4 days with tetralabeled tritiated ED resulted in approx 50% increase in mean survival time (ST). Host survival was not dose-dependent beyond 1 uCi, since ST achieved with 5 or 50 uCi was no better than that obtained with 1 uCi. The mean host survival of animals given 1,150 nanog unlabeled ED plus 50 uCi radioactive ED did not differ significantly from vehicle controls. No effect on host ST was found when comparable amounts of nonradioactive ED were administered for 4 days. Radioactive ED administration for 14 days at dosages of 0.2-2.0 uCi/day resulted not only in a significant increase in animal ST, but also in a significant inhibition of TG. When 0.2 uCi of radioactive progesterone (PG) or radioactive ED were injected per day to C57BL/6J female mice inoculated with BW 10232 tumor cells, TG rate was inhibited by 85% after only 2 days' treatment with [3H]ED. After 8 days' treatment, the inhibitory effect on TG rate declined to 36% and remained at this level until 12 days post hormone injection. As a result of radioactive ED administration for 14 days, ST in these tumor bearing mice was enhanced by 75%. Radioactive PG had no effect on these measurable parameters. Results indicated that further treatment with radioactive ED injections over a longer period of time may extend host survival as well as TG inhibition. (17 Refs)

5. RAT HEPATOMAS: CHEMOTHERAPY WITH LYCURIM AND PYRAZOFURIN.

Lui MS, Jackson RC, Harkrader RJ, Weber G
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JNCI; 68(4):665-668 1982

Hepatoma 8999 was sensitive to Lycurim [1,4-di(methylsulfonyloxy-ethylamino)-1,4-dideoxy-ms erythritol] with a mean lethal dose (LD50) of 8.1 x 10(-8) M for a 6-hr treatment in vitro. The drug dose lethal to 10% of the rats with Lycurim (10 mg/kg) injected ip 12 times into hepatoma 8999-bearing BUF rats at 10-day intervals provided a mean increase in life-span (ILS) of 156%. The more rapidly growing, less differentiated hepatoma 3924A was 10-fold less sensitive to Lycurim in vitro, and three treatments in vivo (10 mg/kg given every 8 days) gave an ILS of only 18% in ACI/N rats. Because hepatoma 8999 had a high adenosine kinase activity, the effect of Pyrazofurin (PF; 3-beta-D-ribofuranosyl-4-hydroxypyrazole-5-carboxamide) was examined in vitro The LD50 was 8.5 x 10(-8) M in a 6-hr exposure. In hepatoma 3924A, with a 15-fold lower adenosine kinase, the LD50 was 22-fold higher. Three treatments with PF (4 mg/kg given every 2 days) in hepatoma 8999 caused an 18% ILS and no host toxicity, but in hepatoma 3924A no significant ILS was observed. Lycurim combined with PF (0.05 uM each) in heptoma 8999 cells in vitro provided synergistic kill, but Lycurim and PF (0.3 and 1 uM, respectively) in hepatoma 3924A cells yielded summation. When 10 rats with hepatoma 8999 were treated 15x with the optimal dose of Lycurim (7.5 mg/kg every 10 1/2 days), 1-yr survivors numbered seven. Alternate doses of Lycurim (7.5 mg/kg) and PF (3 mg/kg) at 5-day intervals for 4 mo to 10 rats gave an ILS of 152% with eight 1-yr survivors and no host toxicity. (Author abstract) (20 Refs)

6. EFFECT OF LIPOSOMALLY TRAPPED ANTITUMOUR DRUGS ON A DRUG-RESISTANT MOUSE LYMPHOMA IN VIVO.

Richardson VJ, Ryman BE
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Br J Cancer; 45(4):552-558 1982

A TLX-5 mouse lymphoma which was resistant to 1-beta-D-arabinofuranosyl cytosine (AraC) was used in vivo to study the possibility of using liposomes as drug-delivery vehicles in order to overcome drug resistance. The effects of free drugs (AraC, AraCTP and methotrexate) and the liposomally associated drugs on the survival time of tumor-bearing mice were determined. As a more sensitive measure of cell survival, 125IUdR was incorporated into the DNA of the ascites TLX-5 cells before ip injection. Cell survival and the cytotoxic effects of the drugs on the tumor cells were determined by using a double-headed gamma counter to measure the retention of the 125I label. Both AraC and AraCTP, either as the free drugs or liposomally associated, had no effects on the tumor. Due to the lack of response of tumor cells to these drugs, further studies were initiated with free and liposomally associated methotrexate (MTX), a drug to which the cells were known to be sensitive. It was found that the liposomally associated MTX, at a 5-10-fold lower dose than the free drug, was (a) more effective in prolonging the survival of tumor-bearing mice and (b) as effective as the free drug in killing tumor cells (as measured by the 125I retention). In vivo MTX was more effective in the liposomally associated form, whereas liposomally entrapped AraC and AraCTP were ineffective. It is proposed that in vivo liposomally associated drugs may be acting not by actively localizing in the tumor cells, but by the liposomes providing a slow-release drug depot, improving the pharmacokinetic properties of MTX. (Author abstract) (19 Refs)

7. A NEW SUGGESTION FOR THE DESIGN OF RATIONAL ANTICANCER THERAPY: EXPERIMENTAL STUDIES IN MICE.

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Med Hypotheses; 8(3):207-230 1982

The specific target and mode of action of dimethylsulfoxide (DMSO)-complex was investigated utilizing colchicine (CH) and vinblastine sulfate (VS) as model systems. Approx 30,000 mice with varying degrees of inherited susceptibility towards skin tumor formation were used. Parallel studies comprised tumor-production series, light, polarization, and electron microscopy, histochemical and histoquantitative examination, and in vitro analyses on various mixed lipoprotein surface films. The typical effects of CH and VS on normal epidermis (NE) were a high incidence of drug-dependent 'monster cells' (MC), great increase in cytoplasmic vol, strong intracellular vacuolization, and unmasking of a pre-existent or partly newly developed, coarse, partly ruptured, fibrous cytoskeleton. The mode and strength of response of benign epidermal condition (BEC) were in principle similar to those of NE. The alterations in malignant epidermal condition (MEC) caused by CH and VS were a very weak mode of response, sparsness of MC, low degree of intracellular vacuolization, and only slight additional alterations within the cytoskeleton. The alterations developing in NE after exposure to CH, VS and DMSO were distinctly sparser than without DMSO and the pathological mitoses showed a shift towards the c-type mitoses. The alterations provoked in BEC closely resembled those developing in NE. Recovery from the injury was evident at 72 hr. Exposure of MEC to DMSO, CH, and VS changed the originally cytostatic-insensitive malignant cells to highly susceptible. The reaction was extremely vigorous while the cells were injured to such an extent that cytokinesis was not any more possible and the cells were doomed to die, and the response was characterized by morphogenic patterns indicating a high degree of rehydration through over-imbibition with water of the malignant cells. (65 Refs)

8. UPTAKE AND INITIAL EFFECTS OF HARRINGTONINE IN MURINE LEUKEMIC CELL SUBLINES SENSITIVE AND RESISTANT TO VARIOUS CHEMOTHERAPEUTIC AGENTS (MEETING ABSTRACT)

Chou TC, Schmid FA, Feinberg A, Philips FS, Han J
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Fed Proc; 41(3):1477 1982

Harringtonine was shown to be rapidly taken up by L1210/0 cells using a fast mixing, fast separating technique and retained with slow rate of release to the medium. Cells resistant to vincristine (L1210/VCR) showed severely impaired capability to take up the drug. Its uptake in L1210 sublines is: L1210/0 greater than L1210/cyclophosphamide greater than L1210/arabinosylcytosine greater than L1210/adriamycin greater than L1210/5-fluorouracil greater than L1210/VCR. [3H]-Leu incorporation into protein in L1210/0 cells was inhibited 90% within 20 min by 0.5 ug/ml of harringtonine; incorporation of [3H]dThd (thymidine) into DNA and [3H]Cyd (cytidine) into

RNA was much less inhibited and showed an apparent lag of onset for 5 and 10 min, respectively. The efficacy of harringtonine in increasing the lifespan of BD2F1 mice bearing the sublines is: L1210/0 greater than L1210/cyclophosphamide greater than L1210/5-fluorouracil greater than L1210/arabinosylcytosine greater than L1 210/adriamycin greater than L1210/VCR. These results suggest that 1) protein synthesis is the primary initial target for the effect of harringtonine and 2) cellular uptake of harringtonine, except in L1210/5-FU, is correlated with therapeutic efficacy. (no Refs)

ANTITUMOR AGENT EFFICACY IN VITRO

9. GROWTH AND CELL SURVIVAL FOLLOWING TREATMENT WITH ESTRAMUSTINE, NOR-NITROGEN MUSTARD, ESTRADIOL AND TESTOSTERONE OF A HUMAN PROSTATIC CANCER CELL LINE.

Hartley-Asp B, Gunnarsson PO
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J Urol; 127(4):818-822 1982

Estramustine at concentrations ranging from 3-40 x 10(-6) M inhibited the cell growth and clonogenic survival of a human prostatic carcinoma cell line (DU 145). This cell line was found to be unresponsive to estradiol and testosterone at concentrations ranging from 10(-9) M to 5 x 10(-5) M. Metabolism studies with estramustine showed that only a few per cent of the ester linkage was cleaved during the exposure period. This small amount of metabolism could possibly lead to the release of nor-nitrogen mustard, which was however found not to be as inhibitory as estramustine in this cell line. The results indicate that estramustine per se causes the cell death of hormone unresponsive human prostatic carcinoma cells in cell culture. (Author abstract) (28 Refs)

10. LIPOSOMALLY TRAPPED ARACTP TO OVERCOME ARAC RESISTANCE IN A MURINE LYMPHOMA IN VITRO.

Richardson VJ, Curt GA, Ryman BE
Dept. Microbiology, Univ. Birmingham, Birmingham B15 2TT, England
Br J Cancer; 45(4):559-564 1982

Two cell lines, one sensitive and one resistant to the cytotoxic effects of cytosine arabinoside (AraC) were studied in vitro as a drug-resistance model. The sensitivity of these cell lines, to the effects of free and liposomally trapped AraC and AraCTP as well as empty liposomes alone and mixed with free drug, was studied. This was done by following the inhibition of [3H]-dT incorporation into cellular DNA during exposure to the various drugs and liposomes. Some of the liposomal-lipid compositions inhibited [3H]-dT incorporation at very low concentrations, which made them unsuitable for further study. Liposomes composed of a 7:2:1 molar ratio of phosphatidylcholine:cholesterol:phosphatidic acid were selected as a suitable non-inhibitory carrier. Sensitivity of the two cell lines to free AraC differed by three logs, when compared in the [3H]-dT-incorporation assay. The resistant cell line was studied further, and was found to be up to three logs more sensitive to AraCTP when given in liposomes than to either the free drug alone or mixed with empty liposomes. It appears from these studies that liposomes are able to help overcome drug resistance in this cell line in vitro. (Author abstract) (25 Refs)

11. D-ALPHA TOCOPHEROL SUCCINATE (VIT E-S) AND HUMAN NEUROBLASTOMA (MEETING ABSTRACT)

Helson L, Verma M
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Am Soc Clin Oncol; 1:C-75 1982

With respect to cancer, Vitamin E is generally thought of as an antioxidant whose major activity is to reduce free radicals associated with carcinogenic activity. Based upon reports of animals tumors sensitivity to Vit E-S by K Prasad we tested three vitamin preparation's antitumor activity on an uncloned human neuroblastoma cell line SK-N-Dz. D-alpha tocopherol in Emulphor EL-620 were no more active than their vehicles. Ethyl alcohol used to solubilize Vit E-S in concentrations as high as 2% did not affect cultured tumor cells. Using an in vitro microtiter assay technique or cells grown in 75 cm2 flasks, Vit E-S in alcohol was added to culture media in final concentrations of 20-200 ug/ml with 0.2%-2.0% alcohol respectively. Within 48 hours significant antitumor activity, ie, lysis, cell growth inhibition and inhibition of 3H-thymidine incorporation occurred at concentrations greater than 50 ug/ml. Cells exposed to Vit E-S greater than 100 ug/ml for 24 hours were irreversibly damaged while no antitumor effects were noted below 25 ug/ml. 3H-uridine incorporation into RNA was not effected. At sublethal concentrations causing less than 100% kill, cell growth was temporarily perturbed with rapid regrowth of remaining cells. After single intravenous (IV) injection of D-alpha (methyl-3H) tocopherol its distribution in nude mice bearing the neuroblastoma SK-N-Dz was; lung greater than liver greater than spleen greater than kidney greater than brain greater than muscle and tumor. The IP route distribution was spleen greater than eye greater than lung greater than kidney, liver and brain. (1 Ref)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

12. RAPID ASSAY FOR EVALUATING THE CHEMOSENSITIVITY OF HUMAN TUMORS IN SOFT AGAR CULTURE.

Tanigawa N, Kern DH, Hikasa Y, Morton DL
Div. Surgical Oncology, UCLA Sch. Medicine, Ninth Floor, Factor Building, Los Angeles, CA, 90024
Cancer Res; 42(6):2159-2164 1982

Assays that measure [3H]thymidine incorporation by cells plated in soft agar were investigated to identify a rapid method for assessing chemosensitivity of tumor cells. Six established cell lines (5 melanomas and 1 colon carcinoma) and cells prepared from 23 primary or metastatic tumors (10 melanomas, 5 colon adenocarcinomas, 3 lung carcinomas, 2 ovarian adenocarcinomas, 1 breast adenocarcinoma, and 1 leiomyosarcoma) were tested. The end point of tritium incorporation was measured by autoradiographs (labeling index) and scintillation counting (cpm) after 24-hr labeling. When results were compared, there was a strong correlation between the two assays (p less than 0.0001). However, the scintillation counting assay had major advantages: (a) counting incorporated radioisotope was technically easier than the autoradiographic method; (b) the DNA synthesis rate of the whole tumor cell population could be evaluated, not that of tumor colony-forming cells alone; and (c) the sampling error was minimized since the procedure was done automatically. There was significant association between cpm values 48 to 72 hr after plating and the number of colonies formed at 2 to 4 wk in control dishes (p less than 0.001). Eighteen of 23 surgical specimens (78%) and all four cell lines were evaluable. Chemosensitivity was assessed after 48 hr of plating with alkylating agents, antibiotics, and Vinca alkaloids and after 72 hr with 5-fluorouracil and methotrexate. Results suggested that an 80% or greater reduction of [3H]thymidine incorporation was correlated with a 75% or greater decrease in colony growth (p less than 0.0001). Thus, this scintillation assay accurately predicted drug-tumor interactions within 5 days that resulted in a 75% or greater decrease in colonies. (Author abstract) (28 Refs)

13. EFFECT OF MISONIDAZOLE OR METRONIDAZOLE PRETREATMENT ON THE RESPONSE OF THE RIF-1 MOUSE SARCOMA TO MELPHALAN, CYCLOPHOSPHAIDE, CHLORAMBUCIL AND CCNU.

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Br J Cancer; 45(3):447-455 1982

The effect has been studied of adding either misonidazole (MISO) or metronidazole (METRO) to cytotoxic drug treatment of C3H mice bearing the RIF-1 sarcoma. The nitroimidazoles were injected 30 min before the cytotoxic drugs at a dose of 2.5 mmol/kg. Both clonogenic-cell survival and growth delay were measured as indicators of tumor response and depression in WBC count and acute lethality were used to indicate normal-tissue response. For melphalan, neither pretreatment agent produced any change in tumor response. For cyclophosphamide, no change was produced by METRO but a minimal increase in tumor response occurred with MISO. An enhancement of cell killing by lomustine (CCNU) was seen with MISO pretreatment, but there was no increase in tumor growth delay. METRO, however, did not enhance tumor response by either endpoint. WBC depression by CCNU was not enhanced by MISO pretreatment, and there was no significant reduction in the acute LD50. This indicates a therapeutic advantage from the addition of MISO to CCNU in this model system. For chlorambucil, considerable enhancement of tumor response followed either MISO or METRO pretreatment (dose-modifying factors of 2.0 and 1.4 respectively). However, the modification by MISO of normal-tissue response to chlorambucil was also enhanced by about a factor of 2, with no therapeutic gain. (Author abstract) (17 Refs)

14. IN VITRO EXPERIMENT ON COMBINATION EFFECT OF CHROMOMYCIN-A3 AND AMPHOTERICIN-B.

Miyamura S, Fujita M

Dept. Cytology, Niigata Univ. Sch. Medicine, Niigata, Japan

Jpn J Antibiot; 34(1):108-111 1981

Cytotoxic and antibacterial effects of a combination of chromomycin-A3 (C-A3) and amphotericin B (AB) were studied in HeLa cells and against bacillus subtilis ATCC 6633 with the aid of agar plate diffusion (APD) and serial dilution (SL) methods. The APD method showed individual and combined cytotoxic effects of C-A3 and AB against HeLa cells; the effects of C-A3 alone were especially marked. Synergistic effects of the two drugs were observed for both cytotoxic and antibacterial experiments with the HeLa cells. Effective action was observed with 0.013-0.05 ug/ml of the C-A3 and 1.22-78 ug/ml of the AB. (5 Refs) (In JPN)

15. GROWTH DELAY IN SMALL EMT6 SPHEROIDS INDUCED BY CYTOTOXIC DRUGS AND ITS MODIFICATION BY MISONIDAZOLE PRETREATMENT UNDER HYPOXIC CONDITIONS.

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Br J Cancer; 45(4):565-570 1982

Experiments have been carried out to determine whether the growth delay induced in small EMT6 spheroids (approx 250 um in diameter) by a range of cytotoxic drugs can be increased by pre-incubation of the spheroids under hypoxic conditions with misonidazole (MISO). Hypoxic pre-incubation was for 3 or 5 hr in the presence of 5 mM MISO, and caused a growth delay of about 1 day or 2 days respectively. Sensitization to nitrogen mustard (HN2), melphalan, chlorambucil, carmustine (BCNU) and lomustine (CCNU) was seen, but the shapes of the dose-response curves and the ratio of effects for 3 hr and 5 hr pretreatment varied between the drugs. In contrast to the other agents, hypoxic pre-incubation with MISO reduced the spheroid response to adriamycin. (Author abstract) (10 Refs)

16. MECHANISM OF SYNERGISTIC CYTOTOXICITY BETWEEN NUCLEOSIDES AND ARABINOFURANOSYL CYTOSINE (ARA-C) AGAINST HL-60 CELLS (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:865 1982

It is known that Deoxyguanosine (dGuo) and ara-C synergistically inhibit cloning of the human leukemia cell lines HL-60 and K562. We have investigated the mechanism of synergy, comparing the effect of dGuo to that of thymidine (dThd), which increases ara-C triphosphate (ara-CTP) pool size and augments incorporation of ara-C into nucleic acid in other cell lines. We incubated log phase HL-60 cells with 0.1 mM dGuo or 1 mM dThd, concentrations equitoxic for HL-60 cloning, for 24 hrs and analyzed changes in cell cycle and deoxycytidine triphosphate (dCTP) pool size. Both nucleosides increased cellular vulnerability to ara-C and caused partial synchrony in early S phase as shown by flow cytometry. dGuo (0.1 mM) reduced dCTP pool size by 29%, as measured with the Escherichia coli DNA polymerase assay, versus a 61% reduction by dThd (1 mM). In subsequent experiments, we analyzed ara-C metabolism by co-incubating HL-60 cells with 10nM 3H-ara-C, a concentration which does not inhibit cell cloning in absence of deoxynucleosides, and with dGuo or dThd in concentrations from 0.01 to 5.0 mM. dThd increased incorporation of 3H-ara-C into DNA, with a maximal increase of 370% at 1.0mM. As assayed by high pressure liquid chromatography, dThd increased ara-CTP pool size up to a maximum of 145% of control at 0.6 mM. dGuo also increased ara-CTP pool size to a maximum of 193% of control at 0.01 mM, the lowest concentration tested. However, dGuo increased incorporation of ara-CTP pool size to a maximum of 193% of control at 0.01 mM, the lowest concentration tested. However, dGuo increased incorporation of ara-C into DNA only marginally (129% of control) at 0.01 mM, and reduced incorporation at higher concentrations. These data suggest that dGuo and dThd exhibit synergy with ara-C by different mechanisms, since dThd augments its incorporation into DNA, while dGuo does not. (1 Ref)

17. INTENSIFIED REMISSION INDUCTION AND CONSOLIDATION WITHOUT MAINTENANCE THERAPY FOR ACUTE MYELOID LEUKEMIA (AML) (MEETING ABSTRACT)

Buchner T, Hiddemann W, Urbanitz D, Kamanabroo D, Schulte H, Van de Loo J

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Proc Am Soc Clin Oncol; 1:C-525 1982

High remission rates in AML achieved by intensive induction therapy induce an increasing therapeutic impact on maintaining remission. We here report on the results of a 9-day induction regimen combining cytosine arabinoside, daunorubicin, and thioguanine at a special time sequence followed by one or two identical consolidations in CR (complete remission) and no further maintenance therapy. Ninety-three pts with a mean age of 48.3 (15-74) years were treated, 22 pts being 60 years or older. Overall CR rate was 71% with 76% of all CRs after one induction course. In the older age group 50% achieved a CR, 92% by one course, only. Median remission duration is 13.4 months for all pts with 23 pts in first CR for 3 to 29 months at a median observation time of 12 months. Median remission duration was significantly dependent on the number of induction courses needed for CR (one cycle 18.6 months, two cycles 7.8 months). These data indicate that by intensified induction and consolidation therapy without maintenance a high CR-rate and an acceptable CR-duration are achieved. Rapid response to only one induction cycle and consolidation, both factors being present in 58% of all responders, were found strong prognosticators for CR duration being 20 months in this group. The subgroup of pts between 15 and 40 years has a median CR duration of 23.2 months, even. (1 Ref)

18. SYNERGISTIC EFFECTS BETWEEN SODIUM WARFARIN OR SODIUM HEPARIN AND ANTICANCER AGENTS ON RAT C6 GLIOMA CELLS (MEETING ABSTRACT)

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Fed Proc; 41(3):1477 1982

Colony formation experiments were utilized in this project to assess the cytotoxicity of anticoagulant and anticancer drugs on C6 glioma cells in culture. Cells were treated with sodium warfarin (W) (10(-3) M) or sodium heparin (H) (63 units per plate) for 24 hrs and were then incubated for 2 hrs with an anticancer agent. Anticancer agents tested included: BCNU (carmustine) (9.3 x 10-6M), busulfan (Bu) (2x10(-5) M), chlorambucil (Ch) (1.6 x 10(-5) M), 5-fluorouracil (FU) (7.7 x 10(-7) M), methotrexate (M) (2.2 x 10(-5) M), vincristine (Vi) (1.2 x 10(-7) M), and VM26 (VM) (7.6 x 10(-7) M). Survival fractions from each 2-drug combination were compared to the effects observed with each drug alone to determine whether each drug combination produced additive cytotoxic, less than additive cytotoxic, or greater than additive cytotoxic effects on the cells. Drug combinations producing additive effects included: Bu+W, Bu+H, FU+W, FU+H, M+H, and Vi+H. Less than additive effects were observed with Vi+W and VM+W. Greater than additive effects were produced by : BCNU+W, BCNU+H, Ch+W, Ch+H, M+W, and VM+H. These in vitro data support the concept of combining anticoagulant and cancer chemotherapeutic therapies in the treatment of selected malignancies. (no Refs)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

19. CHLORPROMAZINE HYPOTHERMIA PROTECTS MICE AGAINST DOXORUBICIN TOXICITY (MEETING ABSTRACT)

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Fed Proc; 41(3):1715 1982

Both membrane fluidity and temperature have been implicated in doxorubicin effects. Since chlorpromazine can affect both body temperature and membranes, we tested it as a protective agent against doxorubicin toxicity. Groups of 10 female mice received chlorpromazine (5 mg/kg sc), followed 1 hr later by doxorubicin (20 mg/kg ip). Rectal temperature decreased to 30C 1 hr after chlorpromazine, and to 28C after 4 hr, returning to normal within 24 hr. In two experiments, chlorpromazine pretreatment decreased 14 day doxorubicin mortality from 60% to 10 and 0%. Chlorpromazine pretreatment also partially reversed the weight loss or slowing of growth produced by lower doxorubicin doses (10 and 5 mg/kg). The results suggest that hypothermia during the period of administration protects against the toxicity of doxorubicin; however, the possibility of a direct chlorpromazine effect cannot be eliminated by the present results. (no Refs)

20. MODULATION OF THE TOXICITY AND ANTITUMOUR ACTIVITY OF ALKYLATING DRUGS BY STEROIDS.

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Br J Cancer; 45(3):413-420 1982

The steroids prednisolone and progesterone significantly altered the therapeutic indices of the alkylating agents, nitrogen mustard, melphalan, cyclophosphamide, phenyl acetic mustard and chlorambucil. For nitrogen mustard, chlorambucil and phenyl acetic mustard, prednisolone reduced host toxicity in the rat and enhanced the antitumor effectiveness against alkylating-agent-resistant strains of the Yoshida sarcoma and Walker carcinosarcoma. Progesterone also increased the therapeutic index of chlorambucil in the rat by decreasing its systemic toxicity. Two other alkylating agents, melphalan and cyclophosphamide, exhibited lower therapeutic indices in combination with prednisolone against alkylating-agent-sensitive tumors. This was due to the greater host toxicity of the combination than of the alkylating agent alone. In alkylating-agent-resistant tumors, however, a significant increase in growth delay was achieved if prednisolone was combined with the alkylating agent. (Author abstract) (44 Refs)

21. EFFECT OF COENZYME Q10 AND VITAMIN B2-BUTYRATE TO ANTICANCER ABILITY AND LIPID PEROXIDATION OF ADRIAMYCIN.

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Kurume Igakkai Zasshi; 44(9/10):678-683 1981

Adriamycin (ADM), a potent anticancer antibiotic, is known to induce severe cardiotoxicity as a side-effect. The pathogenesis of the cardiotoxicity has not been dissolved yet, however, the lipid peroxidation generated by administration of ADM is considered as one of the major mechanisms of tissue damage. The combination use of CoQ10 or B2-butyrate with ADM was found to diminish the lipid peroxidation generated by ADM. In our present paper, it was discussed if the combination use of vitamin B2-butyrate or CoQ10 does not diminish the ability of ADM to inhibit DNA synthesis in Ehrlich ascites tumor cells using incorporation of 3H-thymidine. Vitamin B2-butyrate and CoQ10 inhibited the production of lipid peroxide in Ehrlich ascites tumor cells treated with ADM. In addition, it was apparent that the anticancer ability of ADM was not affected by combination use of antioxidant. From these results, the combination use of vitamin B2 and CoQ10 with ADM was found to be useful in preventing or minimizing the side-effect of ADM. (Author abstract) (16 Refs) (In JPN)

22. EFFECT OF INTRAVESICAL INSTILLATION OF CYTOSTATIC AGENTS ON THE NORMAL EPITHELIUM.

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Urologe [A]; 21(2):116-117 1982

Adriamycin (ADM: 2 mg/ml), mitomycin (MMC: 2 mg/ml), cisplatin (DDP: 2 mg/ml), and ifosfamide (HOL: 100 mg/ml) were administered to 30 female Wistar rats each every 3 days (0.25 ml) until 10 instillations were reached. Each dose was retained for 30 min. Physiologic solution was administered the same way to 20 control animals. Thirty days after last instillation, animals were killed, bladder tissue examined and evaluated for presence of epithelial tumors (ET), epithelial metaplasia (EM), and epithelial proliferation (EP). Eighteen controls could be evaluated and all had normal tissue. Twelve rats treated with ADM could be evaluated: 1 had ET, 5 had EM, 5 had EP, and 4 had normal tissue. Eighteen rats treated with MMC could be evaluated and the results were 4, 12, 9, and 6, respectively. Thirteen rats treated with DDP could be evaluated and the following results were obtained 2, 4, 5, 8, respectively. Three rats treated with HOL could be evaluated and the results were 1, 1, 1, and 2, respectively. This effect was dependent on the dose administered. No effect was observed when 0.1 mg/ml was administered 10x or 0.1, 0.5, or 2.5 mg/ml were administered 1x or 3x as shown in a prior work. (18 Refs) (In GER)

23. COVALENT PROTEIN BINDING OF REACTIVE ADRIAMYCIN METABOLITES IN RAT LIVER AND RAT HEART MICROSOMES.

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J Cancer Res Clin Oncol; 103(1):39-48 1982

Covalent binding of 3H-labeled adriamycin metabolites to bovine serum albumin and microsomal protein is demonstrated in an aerobic incubation system with rat liver and rat heart microsomes, respectively, using exhaustive organic solvent extraction and gel chromatography. Covalent protein binding was dependent on active microsomes, NADPH, and oxygen and was inhibited by reduced glutathione and other sulfhydryl compounds. The anthracycline moiety was spectrophotometrically evidenced in the adriamycin metabolite(s) covalently bound to protein. Thus, enzymatic activation of adriamycin in the heart with consecutive covalent protein binding of reactive adriamycin semiquinone radicals may contribute to adriamycin cardiotoxicity. (Author abstract) (48 Refs)

24. EFFECTS OF BLEOMYCIN ON PROSTAGLANDIN SYNTHESIS AND DEGRADATION IN HAMSTER (MEETING ABSTRACT)

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Fed Proc; 41(3):1079 1982

Circulating levels of PGs have been demonstrated to change following exposure to various lung toxins. Since the lung is active in the synthesis and degradation of PGs (prostaglandins), changes in either its ability to synthesize and/or metabolize PGs may affect circulating levels. Thus, we characterized and studied the effect of bleomycin, a lung toxin, on the in vitro synthesis and degradation of PGs in hamsters. PG synthesis by hamster lung microsomal protein exhibited linearity with incubation times from 10 to 30 minutes and 50 to 200 ug protein. Following intratracheal instillation of 1 unit of bleomycin it was found that, on a per lung basis, there was a significant increase in the protein content of the 105,000 g supernatant at all times. In contrast, the microsomal protein content was only significantly elevated at 4, 14 and 21 days after treatment. Degradation of PGs was generally elevated at all times with significant increases at 4 and 7 days post-treatment. Accompanying these changes significant elevations in the synthesis of PGF2alpha and PGD2 were observed at 2, 7 and 21 days and 2, 4 and 21 days after treatment, respectively. In addition, synthesis of PG 6-Keto-F1alpha was significantly increased at 7 and 21 days and TxB2 (thromboxane B2) at 4 days following bleomycin treatment. However, PGE2 synthesis remained unchanged. (no Refs)

25. A COMPARISON OF THE PULMONARY TOXICITY PRODUCED BY METAL-FREE AND COPPER-COMPLEXED ANALOGS OF BLEOMYCIN AND PHLEOMYCIN.

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Toxicol Appl Pharmacol; 63(3):351-362 1982

The contribution to pulmonary toxicity of the thiazole rings was evaluated by comparing the pulmonary toxicity of bleomycin (BLM) and phleomycin (PLM) with analogous terminal amines. The role of surface metal binding sites in the production of pulmonary toxicity was examined by comparing the effects on the lung of metal-free and copper-complexed analogs of bleomycins and phleomycins bearing identical terminal amines. Doses of all compounds were 1 and 10 nanomole, dissolved in 50 ul, and administered as a single endotracheal dose to retired breeder male DBA/2J mice (28 wk old). The morphologic changes (interstitial fibrosis, confluent fibrosis, epithelial metaplasia, and extensive disease) induced by metal-free and copper-complexed 1[[4-((3[4-(3-(4-aminobutyl) guanidine)butyl]guanidino)butyl]]guanidine - -bleomycin (BLM B6) or -phleomycin (PLM G), and N'-(1-phenylethyl)-N-(3-aminopropyl)-1,3-diaminopropyl bleomycin or -phleomycin were similar. There was also no distinguishable difference in pulmonary toxicity between bleomycin and phleomycin analogs with identical terminal amines: BLM B6 or PLM G and N-cyclohexyl-1,3-diaminopropyl-BLM or -PLM. Therefore, hydrogenation of the thiazole ring does not contribute to pulmonary toxicity. These findings, combined with those related to presence and absence of copper support the importance of the terminal amine substituents as determinants of lung injury. (38 Refs)

26. NEUROTOXICITY OF QUELAMYCIN IN THE RAT.

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Neurotoxicology; 2(4):789-792 1981

Single doses of 10 or 20 mg/kg quelamycin were injected iv into male Sprague-Dawley rats; samples of dorsal root ganglia (DRG) obtained 4, 12, 28, and 48 days after administration were examined by light microscopy. Loss of toluidine-blue stainability of the neurons was found in all animals at day 4 and involved 50-60% of the DRG neurons; other cytoplasmic abnormalities and some necrotic neurons were also observed. The frequency of neuronal changes declined at later sampling times. The neurotoxic effect of quelamycin is qualitatively similar to but less severe than that of its parent compound adriamycin. (14 Refs)

27. ALTERATIONS IN HEPATIC AND RENAL LEVELS OF GLUTATHIONE AND ACTIVITIES OF GLUTATHIONE S-TRANFERASES FROM RATS TREATED WITH CIS-DICHLORODIAMMINEPLATINUM-II.

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Cancer Chemother Pharmacol; 8(1):67-71 1982

The effect of cis-dichlorodiammineplatinum-II (cisPt) treatment on a variety of glutathione (GT)-dependent enzymatic pathways, endogenous levels of GT, and a possible in vivo association between platinum and GT was studied in female Sprague-Dawley rats. The effects of cisPt treatment on the activity of glutathione-dependent transferases and amounts of GT in post-microsomal supernatants of liver and kidney are presented. The only consistent and noteworthy change was a decrease in GT in the liver. Activity of glutathione-S-aryltransferase [substrate: 3,4-dichloronitrobenzene (DCNB)] was increased 2-4x at 5, 8, and 12 days post-treatment. Effects at earlier times were variable and time-dependent. At the same time that DCNB was significantly increased, the activity of glutathione S-epoxidetransferase was significantly decreased. Total GT was increased by 3-5x normal at 8 and 12 days post-treatment, but by lesser amounts at earlier times. At all times except day 3, glutathione reductase was decreased. When various concentrations of cisPt were added in vitro to cytosol from control rats and the tissue allowed to stand for up to 2 hr, few consistent, dose-related changes in enzyme activity were observed. In rats treated for 1 hr with cisPt, the liver and kidney contained 94-98% acid-insoluble proteins. In both liver and kidney, the amount of platinum retained after acid addition was lowest for crude homogenate (48-54%), while the cytosol retained larger amounts of platinum (94-111%). When protein and platinum concentrations were studied 30 hr after animal treatment or 12 hr after in vitro addition to control homogenates, qualitatively similar results were obtained. (33 Refs)

28. PRONOUNCED INHIBITION OF CALMODULIN BY PLATINUM COMPLEXES (MEETING ABSTRACT)

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Fed Proc; 41(3):504 1982

It is known that cis-Diamminedichloroplatinum (II) (c-Pt), a compound with antineoplastic activity, is particularly effective for treatment of testicular and ovarian cancers. It is also promising in therapy of brain tumors. Its use, however, is limited by adverse effects, especially nephrotoxicity. Calmodulin (CaM) is present in high levels in testis and brain, mediating many of the effects of Ca++, which controls key cellular processes, including chromosome movement and cell division. We investigated the potential effect of c-Pt on CaM using phosphodiesterase to monitor its activity. c-Pt does not affect CaM activity; however, its 'aquo'-derivative is a potent inhibitor. The drug did not alter basal phosphodiesterase activity. Kinetic experiments showed that the 'aquo'-derivative at micromolar concentrations abolishes CaM activity within a few hours. Ca++ protects CaM from inactivation. Inhibition could be reversed by thiourea, 2,3-dimercaptopropane sulfonate and diethyldithiocarbamate. The drug-inactivated CaM did not show the characteristic Ca++-dependent conformational changes. The 'aquo'-derivative of trans-platinum is ineffective as an anti-neoplastic agent, but was equally potent in suppressing CaM activity. This suggests that CaM inhibition by c-Pt is not central to its antineoplastic activity; however, it may constitute a basis for drug toxicity. (no Refs)

29. SPERMATOGENIC STAGE SENSITIVITY TO 6-MERCAPTOPURINE IN THE MOUSE.

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Mutat Res; 94(1):165-178 1982

The effects of 6-mercaptopurine on the rate of spermatogenesis in hybrid (101 x C3H) male mice 12-13 wk old were investigated. These mice were given [3H]thymidine ip and 1 hr later 150 mg/kg MP in 0.03 N sodium hydroxide. Spermatogonial counts at 72 hr revealed cell killing of only A1, A2, and A3 spermatogonia with respective decreases of A2-A4 gonia to 81%, of In cells to 53%, and B spermatogonia to 50% of control. There was an abrupt change in survival with development of A3 into A4 spermatogonia, because late A4-In cells were 98% of control. The only effect at 10 days was a slight reduction in A1-B spermatogonia in the previous cycle of the seminiferous epithelium. There were 67 cells with bridges, fragments, and bridges + fragments in a total of 2,012 apparently viable anaphase I figures and a total of 188 cells with bridges and fragments in a total in 1,175 degenerating anaphase I figures. In anaphase II there were 36 cells with bridges, fragments, or bridges + fragments in 2,061 viable cells, and 106 abnormal divisions in 1,182 degenerating cells. Thus, the frequency of chromosome aberrations in degenerating spermatocytes was four times that observed for viable cells at anaphase I and five times that observed for viable secondary spermatocytes in anaphase II. Combined treatment with 150 rad x-rays and MP gave an additive effect and demonstrated that the peak incidence of dead implants observed at 30.5-35.5 days is due to cells treated as preleptotene spermatocytes and must result from cytologically undetectable genetic damage. (17 Refs)

30. THE KINETICS OF THE PROTECTIVE EFFECT OF BETA-SITOSTEROL AGAINST MNU-INDUCED COLONIC NEOPLASIA.

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J Cancer Res Clin Oncol; 103(1):49-54 1982

The effect of dietary supplementation with beta-sitosterol (0.2% of diet) was followed in Fischer rats after both acute and chronic feeding. Compared to controls after 3 and 7 days, the number of epithelial cells per crypt column in both plant sterol fed groups was shifted to lower values; moreover, fewer cells above cell position 12 were engaged in DNA synthesis. Continued feeding of beta-sitosterol for 28 wk revealed the number and position of 3HTdR-labeled cells per crypt column after 1 hr pulse labeling to be similar to that seen in the acute phase. However, differences were more marked after 24 hr showing the max number of labeled cells per column to be at least 25% less than the untreated group and the leading edge of labeled cells moving more slowly up the crypt wall. Rats treated with N-methyl-N-nitrosourea (MNU) intrarectally (8 mg/animal) while simultaneously consuming beta-sitosterol demonstrated a reduction in the size of the proliferative compartment as well as the number of labeled cells per crypt column as compared to rodents receiving just the carcinogen (3.3 and 5.4 mean labeled cells per column, respectively). At this time, MNU-treated rats fed beta-sitosterol had a significantly decreased colonic tumor incidence. This plant sterol which passes through the digestive tract relatively unabsorbed appears to slow colonic epithelial cell proliferation resulting in a reduced expression of neoplastic transformation. (Author abstract) (6 Refs)

31. STEM CELL (CFUS) PROLIFERATION INHIBITOR IN BLOOD OF MICE INJECTED WITH HYDROXYUREA.

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Cell Tissue Kinet; 15(3):263-268 1982

Analysis of the mouse hemopoietic stem cell (CFUs) kinetics after hydroxyurea administration has provided an in vivo assay suitable for detection of factors which inhibit recruitment of non-proliferating G0-CFUs into cell cycle, or transit of CFU's through the G1 phase. Using this assay, it has been demonstrated that plasma obtained from mice which had received hydroxyurea approx 12-14 hr previously, possesses a factor which inhibited the triggering of CFUs into the cell cycle. The appearance of this CFUs proliferation inhibitor occurred at a time when 60-70% of the CFUs were synchronized in the S phase of the cell cycle, as a consequence of hydroxyurea action. Some basic properties of the inhibitor were investigated. (Author abstract) (10 Refs)

32. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.

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Eksp Onkol; 4(2):12-19 1982

Incidence of spontaneous and induced tumors of the peripheral nervous system (PNS) in the experimental animals is reviewed. PNS neoplasms were induced after sc or im applications of polycyclic hydrocarbons. Injection of methylcholanthrene into the sciatic nerve produced tumors in rabbits and in random-bred rats. The spectrum of nitrosamine-induced PNS tumors was shown to depend upon the animal species, age, strain, dose, and the mode of administration. Prolonged iv administration of methylnitrosourea (MNU) resulted in selective induction of CNS and PNS tumors. High incidence of neurogenic tumors was recorded in Fisher and BD-IX rats. Ethylnitrosourea (ENU) showed high affinity to PNS during transplacental carcinogenesis. Sensitivity of rat embryo to ENU was 30-50x greater than that of the adult rats. The highest incidence of PNS tumors was observed after ENU administration during the last third of the gestation. Nitroso compounds and urethane were reported to induce tumors of the sympathetic nervous system in rabbits, hamsters, and rats. (103 Refs) (In RUS)

33. STRAIN DIFFERENCES OF TUMORIGENIC EFFECT OF NEONATALLY ADMINISTERED N-ETHYL-N-NITROSOUREA IN RATS.

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Gan; 73(2):323-331 1982

The tumorigenicity of neonatally administered N-ethyl-N-nitrosourea (ENU) was studied in four different inbred strain rats, that is Wistar/Furth (WF), Long-Evans (LE), F1 of Wistar/Furth and Long-Evans (F1) and Fischer 344 (F344) rats. All strains developed tumors of the nervous system with high incidence (97 to approx 100%) during 6 mo of observation. The incidence of tumor of the central nervous system, including the brain (82 to approx 88%) and the spinal cord (53 to approx 76%), was high in all strains, but that of the peripheral nervous system, including the cranial nerve (21 to approx 89%) and the spinal root (13 to approx 93%), differed by strain. The peripheral nervous system of WF and F344 rats had a low susceptibility to the tumorigenic effect of ENU, but that of LE rats had a high susceptibility. Many brain tumors were induced in the temporal and frontal cortex and subcortex in all strains of rats. Spinal cord tumors were observed at all levels of the white matter of the spinal cord without any predilection site. Spinal root tumors were located in lumbosacral plexuses in WF and F344 rats, but in Le and F1 rats cervical and thoracic root tumors were also observed. Histological examination revealed that most of the brain and spinal cord tumors were oligodendroglioma, but in F344 rats about half of the brain tumors were mixed glioma. Epidermoid cysts of the lumbar spinal cord were observed only in F344 rats. Tumors of the peripheral nervous system were so-called anaplastic schwannoma. (Author abstract) (23 Refs)

34. URIDINE RESCUE FROM THE LETHAL TOXICITY OF 5-FLUOROURACIL IN MICE.

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Cancer Chemother Pharmacol; 8(1):17-21 1982

The ability of continuous sc infusion of uridine (Urd), thymidine (dThd), or deoxyuridine (dUrd) to rescue mice from the lethal toxicity of 5-fluorouracil (FUra) was studied in male C57BL/6 x DBA/2F1 mice to determine the relationship between FUra toxicity and its RNA- and DNA-directed actions. To determine the gross toxicity to mice of an sc infusion of Udr, dThd, or dUdr, each nucleoside was administered to mice for 5 days. Treatment of mice with a single ip injection of FUra (800 mg/kg) followed by a 5-day infusion with Urd (0.1 g/kg/day) resulted in no day 30 survivors out of a group of six. Infusions with Urd at 1, 5, or 10 g/kg/day were all effective in rescuing mice from lethal toxicity of FUra. Urd at 5 g/kg/day rescued mice that had been treated with with 400, 600, or 800 mg FUra/kg. However, Udr at 5 g/kg/day was only slightly effective in rescuing mice treated with 1,000 mg/kg FUra, and it was completely ineffective after 1,200 mg/kg FUra. The results indicate that the approx LD10 of FUra was more than tripled by Urd rescue. Treatment of mice with a single ip injection of FUra (800 mg/kg) followed in 24 hr by a 5-day infusion with dThd or dUdr at 1, 5, or 10 g/kg/day did not rescue mice from the lethal toxicity of FUra; the results with dThd and dUdr were no different than those obtained with a 0.9% NaCl infusion. The results support the concept that the RNA- rather than DNA-directed action of FUra is an important determinant of its toxicity in mice. (26 Refs)

35. EFFECT OF MELPHALAN ON DELTA-AMINOLEVULINIC ACID SYNTHETASE ACTIVITY IN RAT SPLEEN, BONE MARROW AND LIVER (MEETING ABSTRACT)

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Fed Proc; 41(3):1476 1982

The effect of melphalan, an antineoplastic alkylating agent known to produce bone marrow depression, on the erythropoietic (bone marrow and spleen) and non-erythropoietic (liver) forms of delta-aminolevulinic acid synthetase (ALA-S) activities was studied. A single oral dose (20 mg/kg) caused a 60% loss of ALA-S activity in spleen and bone marrow 16 hrs after dosing. Loss of ALA-S was maximal at 7 days when the activity was 8% of controls in spleen and 32% in bone marrow. Splenic weight was decreased to 50% in 24 hr and to 15% of controls at 7 days. Total splenic protein content was unaffected at any time period. White blood cell (WBC) count declined rapidly at 16 hr, with a maximal depression at 7 days (12% of controls). Red blood cells, hematocrit and hemoglobin content were decreased only at 7 days to 77% of control. By day 15 splenic and bone marrow ALA-S activities increased to 200% of controls, splenic weight increased to 150% of controls and a shift to the segmented form in the differential WBC count was observed. By five weeks all parameters had returned to control values. Liver ALA-S activity was not appreciably affected at any time point, neither was the content or activity of cytochrome P-450. The results of this study indicate that ALA-S is a possible target site for melphalan within the hematopoietic compartment. (no Refs)

PHARMACOKINETICS OF ANTITUMOR AGENTS

36. ALLOPURINOL KINETICS AND BIOAVAILABILITY. INTRAVENOUS, ORAL AND RECTAL ADMINISTRATION.

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Cancer Chemother Pharmacol; 8(1):93-98 1982

Disposition kinetics of allopurinol (APL) and oxypurinol (OXL), the major metabolite of APL, were examined in six healthy adult males (23-38 yr old) after administration by iv, po, and rectal routes. Each subject received single doses of three different APL dosage forms (500 mg iv, two 300-mg tablets, and two 300-mg suppositories in either cocoa butter or polyethylene glycol). Plasma APL and OXL concentrations were measured over a period of at least 60 hr. After iv dosing, APL was rapidly eliminated from the body, with an av half life (t1/2) of 1.62 hr. After po administration, max plasma concentrations were achieved between 0.5 and 3.6 hr (av 1.95 hr) and the av absolute systemic bioavailability was 67% +-23% (range 41-107%). Neither suppository form gave any measurable plasma concentrations of APL or OXL. The av elimination rate constant for OXL after iv APL was 0.041 +-0.011/hr (range 0.031-0.058/hr), corresponding to a t1/2 of 16.9 hr, similar to the av t1/2 of 19.8 hr after po administration. The large vol of distribution (Vd) of APL, 1.61 liter/kg, suggests substantial extravascular distribution. These results indicate that current use of rectal forms of APL as an adjunct in cancer chemotherapy should be reexamined. (16 Refs)

37. PHARMACOKINETICS OF VP16-213 IN LEWIS LUNG CARCINOMA BEARING MICE.

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Cancer Chemother Pharmacol; 7(2/3):127-131 1982

The pharmacokinetics of VP16-213 (4'-demethylepipodophyllotoxin-(4,6,0-)ethylidene-beta D-glucopiranoside) was investigated in Lewis lung carcinoma bearing C57Bl/6 mice following iv injection at doses of 13 and 40 mg/kg. At both doses, the drug was eliminated from the plasma biphasically with a rapid distribution half-life of 1 and 2 min and an elimination half-life of about 30 min. The highest levels of VP16-213 were found in the liver, small intestine, and kidney. Lower levels were found in the heart, brain, and spleen. Higher levels were found in metastases than in the primary tumor. The AUC (area under the concentration vs time curve) values in some tissues were not proportional to the dose, eg in primary tumor and brain the levels after 40 mg/kg were disproportionately lower than after 13 mg/kg, while in the liver the levels after 40 mg/kg were 12x higher than after 13 mg/kg. This suggests a dose-dependent accumulation of VP16-213 in the liver. Urinary excretion of VP16-213 accounted for 20 and 30% of the doses in the 60 hr after administration of 40 and 13 mg/kg. The cytotoxic effect of VP16-213 on cells from primary tumor and metastases grown in vitro was also investigated. For both the primary tumor and metastases, the cell survival and 3H-thymidine uptake showed a steep concentration response curve in the range of 0.1-10 ug/ml. (10 Refs)

38. THE EFFECT OF ALLOPURINOL (ALLO) ON THE PHARMACOKINETICS OF ORAL (PO) AND PARENTERAL (IV) 6-MERCAPTOPURINE (6-MP) (MEETING ABSTRACT)

Zimm S, Narang PK, Riccardi R, O'Neill D, Chatterji D, Poplack DG
National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:829 1982

It has been recommended that when Allo and 6-MP are used together, the dose of 6-MP should be reduced by 2/3-3/4. We studied the effect of Allo pretreatment on systemic levels of 6-MP in 3 rhesus monkeys following po and IV administration using a reverse phase high pressure liquid chromatography assay that distinguishes 6-MP from thiouric acid and Allo. Single po and IV doses (100mg/m(2)) of 6-MP were administered with and without Allo pretreatment (150mg/M2 IV q 12 hrs beginning 26 hrs prior to 6-MP dosing). The peak levels following a po dose increased from a mean of 4.8x10(-7) (range: 4.6-4.9x10-7M) without Allo to 2.0x10-6M (range: 1.6-2.4x10-6M) after Allo, with a corresponding 4 fold increase in the area under the curve (AUC) - a measure of the amount of drug present in the systemic circulation over time. The time to peak plasma level and the beta half-life were not altered. In contrast to its effect upon po 6-MP, Allo had no effect on the pharmacokinetics of IV 6-MP. This is supported by the lack of a substantial difference between the mean AUC following 6-MP dosing with (558ug ml-1 min) and without (554ug ml-1 min) Allo. Although Allo markedly alters the pharmacokinetics of po 6-MP, it has no effect on IV 6-MP. To gain access to the systemic circulation oral 6-MP must pass through the liver where the drug is metabolized by xanthine oxidase. Allo's inhibition of xanthine oxidase may in part explain the increase in 6-MP plasma levels after oral dosing. While dose reduction of oral 6-MP when given in conjunction with Allo is appropriate, it may not be necessary when Allo is given with IV 6-MP. (no Refs)

39. PHARMACOKINETIC STUDY OF 5-FU: COMPARISON OF DIFFERENT ROUTES OF INTRAHEPATIC ADMINISTRATION IN CANINE MODEL (MEETING ABSTRACT)

Didolkar MS, Jackson AJ, Walker AP, Kalidindi SR
University of Maryland Hospital, Baltimore, MD, 21201
Proc Am Soc Clin Oncol; 1:C-72 1982

Recently, to achieve high concentration of 5-FU (5-fluorouracil) in liver for metastatic adenocarcinoma and least systemic toxicity, different routes of administration have been suggested. However, studies on pharmacokinetics of 5-FU to determine the best route of administration are very few. To determine the method of achieving highest extraction of 5-FU by liver and least 'systemic availability', 5-FU (30mg/kg) was administered as a bolus injection through systemic vein (SV), hepatic artery (HA), hepatic artery after it's proximal ligation (HA + Deart) and portal vein (PV) routes. Samples of blood were taken from inferior vena cava and hepatic vein at 1, 2, 3, 5, 10, 15, 30, 60, 120, and 180 minutes after injection. High pressure liquid chromatographic analysis was done to determine 5-FU levels. Blood flow to liver was measured by electromagnetic flow meter. Mean HA blood flow was 239 ml/min and PV was 240 ml/min. Half life of 5-FU from SV was 7.3 to 31.7 min and from 4V was 6-14.2 min. Mean concentration of 5-FU per unit of time determined by area under the plasma level time curve in microgm/ml/min was: SV 2071, HA 1062.9, HA + Deart 2069.5 and PV 2163. Systemic availability of 5-FU was dependent on the mode of administration and it was 46% for SV, 5% for HA, 37% for HA + Deart and 66% for PV route. Thus we conclude that maximum extraction of 5-FU with least systemic availability was best achieved when it was administered by HA route as compared to SV and PV routes. (no Refs)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

40. CANCER CHEMOTHERAPY MODEL USING AUTOCHTHONOUS OVARIAN CANCER IN RATS. EFFECT OF IFOSFAMIDE ON DMBA INDUCED TUMOR.

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Kurume Igakkai Zasshi; 44(11):731-747 1981

Chemotherapy of DMBA-induced autochthonous ovarian cancer in rats, which is similar to that in human, was studied to evaluate the effect of ip and iv administration of Ifosfamide. DMBA was applied to the ovarian parenchyma of 8-wk-old Wistar rats (clipping method), and adenocarcinomas developed in 131 (48%) of the 273 rats during the 30 wk observation period. Rats with ovarian cancer were performed punch biopsy by exploratory laparotomy and received ip instillation of 50 mg/kg body weight (single shot), 100 mg/kg (single shot), 200 mg/kg (single shot), 50 mg/kg (dialy for 5 days), or iv injection of 40 mg/kg (once a wk for 4 wk), 100 mg/kg (once a wk for 4 wk), 40 mg/kg (dialy for 5 days). At the 5th wk of Ifosfamide administration, all of these rats were sacrificed. All tumors responded to chemotherapy, and in comparison with the non-treated group, various retardation of tumor growth was observed. Various degrees of histological degeneration were found on light and electron microscopical observation. Histological effect was classified by the criterion of Ooboshi-Shimosato, and Grade III or IV which showed necrosis and degeneration of the tumor tissue appeared in the group of iv injection. Morphologically, it seemed likely that the iv dosage produced greater effect rather than the ip dosage. This animal model has been employed intensively to investigate the etiology and pathogenesis of ovarian cancer in humans. Thus, it is probable that chemotherapy against autochthonous ovarian cancer in experimental animals is much closer to the screening of chemotherapy for human cancer. (Author abstract) (29 Refs) (In JPN)

41. IN VITRO MODE OF ACTION, PHARMACOKINETICS, AND ORGAN SPECIFICITY OF POLY (MALEIC ACID-STYRENE)-CONJUGATED NEOCARZINOSTATIN, SMANCS.

Takeshita J, Maeda H, Kanamaru R
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Gan; 73(2):278-284 1982

The organ specificity and pharmacokinetics of SMANCS, poly (maleic acid-styrene)-conjugated neocarzinostatin (NCS), were investigated in rats. The drug activity accumulated primarily in the regional lymph nodes after subcutaneous injection. After intravenous injection, the drug was found in the kidney, lymph nodes, and bladder in very high concentrations, and in lesser concentrations in the bone marrow, lung, small intestine, liver and spleen. The urinary excretion rate and total recovery of the drug after intravenous injection were higher than those after subcutaneous injection. SMANCS, having a mol wt of 2.5 x 10(4) daltons, was degraded in vivo to NCS (mol wt about 1.1 x 10(4)). This was also confirmed in vitro by incubating the drug with cell homogenates. SMANCS caused strand scission of DNA similarly to NCS in lymphoblastoid cells. However, in a cell-free system using colicin E1 plasmid DNA, a high concentration of SMANCS was required to produce DNA degradation detectable by the alkaline sucrose gradient method. (Author abstract) (17 Refs)

42. HUMAN PROSTATIC ADENOCARCINOMA: COMPARATIVE EXPERIMENTAL TREATMENT OF THE TUMOR LINE PC 82 IN NUDE MICE.

Hoehn W, Walther R, Hermanek P
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Prostate; 3(2):193-201 1982

The human prostatic adenocarcinoma PC 82, transplanted into male nude Balb/c mice, produced a newly developing tumor after 4-6 wk. These tumors had a doubling time of about 40 days, from which a volume doubling time of 12.5 days was calculated. Castration resulted in an immediate cessation of growth and a slight decrease in tumor size. Administration of 20 ug/day 17-beta-estradiol to intact males had a stronger effect on tumor progression, and a combination of estrogen + castration produced an even greater effect. Administration of 180 and 300 ug/day of estramustine phosphate (EP) resulted in a slight and variable decrease of the tumor growth rate; in some cases the tumor diameter increased after an initial growth regression. Combination of castration + EP produced a marked decrease in tumor size compared to the treatment with EP only. Administration of cyproterone acetate, in doses of 200 and 400 ug/day, and flutamide (SCH 13521) in a dose of

250 ug/day to intact mice resulted in a weak growth depression which was less than that caused by castration. The histological changes during tumor regression after treatment, eg widened acinar lumina, reduced epithelial height, and vacuolated cytoplasm, are comparable to features seen in treated human prostatic carcinoma. Thus, PC 82 may be a useful model system in comparative studies of new treatment modalities. (35 Refs)

43. STRUCTURE-ACTIVITY RELATIONSHIPS OF NOGALAMYCIN ANALOGUES.

Wiley PF, Elrod DW, Houser DJ, Richard FA
Res. Lab., Upjohn Co., Kalamazoo, MI, 49001
J Med Chem; 25(5):560-567 1982

Nogalamycin (1) has been modified by changes at C-10 and C-7 and in the dimethylamino group to prepare an extensive series of analogues. The chemistry involved in the modifications and structure-activity relationships among these nogalamycin analogues are discussed, as well as comparisons with previously reported compounds 1, 7-con-O-methylnogarol (2), and disnogamycin (11). (Author abstract) (7 Refs)

44. MEMBRANE CARBOHYDRATE ANALOGUES WITH ANTITUMOR ACTIVITY (MEETING ABSTRACT)

Bernacki RJ, Sharma M, Angelino N, Korytnyk W
Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 23:803 1982

We have synthesized several carbohydrate analogues as potential inhibitors or modifiers of cell surface glycoconjugates. These compounds have been tested as antitumor agents in a number of in vitro and in vivo test systems. Two agents, a galactosamine and a mannosamine analogue, have demonstrated significant biological activity. 2-Acetamido-2,4-dideoxy-4-fluoro-1,3,6-tri-O-acetyl galactopyranose, a lipophilic N-acetylgalactosamine analog designed to inhibit carbohydrate chain elongation, inhibited L1210 leukemia cell growth by 50% in vitro at 3.5 x 10-5M. It specifically inhibited the incorporation of D-mannose and L-leucine into L1210 cells at these concentrations. Administration of 50 or 100 mg/kg/day x 5 ip to DBA/2Ha mice with L1210 leukemia increased their life span by over 50%. 2-Amino-2-deoxy-N'-methyl-N'-nitrosoureido-1,3,4,6 tetra O-acetyl-D-mannopyran ose, a lipophilic mannosamine analogue related to streptozotocin, was found to inhibit L1210 cell thymidine incorporation more specifically than sugar incorporation. It inhibited 50% of L1210 cell growth in vitro at 5 x 10-5M. This compound at 30 mg/kg/day x 5 ip cured DBA/2Ha mice with L1210 leukemia and at 50 mg/kg/day x 5 increased the life span of DBA/2J mice by 50%. The effects of both these agents on plasma membrane glycoconjugate structure and formation and their effects on other metastatic tumors in mice are currently being investigated. (no Refs)

45. STRUCTURAL MODIFICATIONS OF ANGUIDIN AND ANTITUMOR ACTIVITIES OF ITS ANALOGUES.

Kaneko T, Schmitz H, Essery JM, Rose W, Howell HG, O'Herron FA, Nachfolger S, Huftalen J, Bradner WT, Partyka RA, Doyle TW, Davies J, Cundliffe E
Res. Div., Bristol Lab., Div. Bristol-Myers Co., Syracuse, NY, 13201
J Med Chem; 25(5):579-589 1982

Approximately 60 derivatives of anguidin were prepared for evaluation of antitumor activities. Positions, 3,4,8-10, and 15 were modified, and the resultant derivatives were screened against P-388 leukemia. It was found that introduction of the C3-keto and C3,C8-diketo groups markedly improved the antileukemic activity, whereas epoxidation of the C9-C10 double bond or oxidation of the C15 position diminished its activity. Selected derivatives were further tested in the L1210, B16, Lewis lung, Colon 36, and Colon 38 tumor lines. Among these compounds, 4beta, 4beta,15-diacetoxyscirpene-3,8-dione (54) and 4beta-(chloroacetoxy)-15-acetoxyscirpene-3,8-dione (55) were found to be most active in various tumors. Inhibitory action of several analogues on protein synthesis was also examined using H-HeLa cells. (Author abstract) (28 Refs)

46. SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL PYRIMIDINE NUCLEOSIDE ANALOGUES OF 1,4-OXATHIANE, 1,4-DITHIANE, AND 1,4-DIOXANE.

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J Med Chem; 25(5):522-526 1982

Nine pyrimidine nucleoside analogues, in which the group attached at N-1 is a six-membered ring containing two heteroatoms, have been synthesized using the Vorbruggen and Bennua coupling procedure. These are 1-(1,4-oxathian-3-yl)-5-fluorouracil (8), 1-(4-oxo-1,4-oxathian-3-yl)-5-fluorouracil (2 stereoisomers 9 and 10, resolved by silica gel column chromatography), 1-(1,4-oxathien-3-yl)-5-fluorouracil (11), 1-(1,4-oxathian-2-yl)-5-fluorouracil (12), 1-(1,4-dithian-2-yl)-5-fluorouracil (15), 1-(1,4-dithian-2-yl)uracil (16), 1-(1,4-dithian-2-yl)thymine (17), and 1-(1,4-dioxan-2-yl)-5-fluorouracil (20). All of the analogues were tested for cell-growth inhibition using mouse and human tumor cell lines. The ID50 values of all of the analogues are greater than 10(-4) M, except in the case of 11 using the L1210 cell line. The most active analogues found are compounds 11 and 17, which were found to be 100 and 200x less active, respectively, than 5-fluorouracil in the human erythroleukemia cell line, K-562. (Author abstract) (34 Refs)

47. ANTITUMOR AGENTS. 2. BISGUANYLHYDRAZONES OF ANTHRACENE-9,10-DICARBOXALDEHYDES.

Murdock KC, Child RG, Lin YI, Warren JD, Fabio PF, Lee VJ, Izzo PT, Lang SA, Angier RB, Citarella RV, Wallace RE, Durr FE

Dept. Chemical Res., American Cyanamid Co., Lederle Lab., Pearl River, NY, 10965

J Med Chem; 25(5):505-518 1982

The compound 9,10-anthracenedicarboxaldehyde bis[(4,5-dihydro-1H-imidazol-2-yl)hydrazone] (bisantrene, VI-1) showed anticancer activity in mice vs both leukemias and solid tumors. Increases in life span vs the following neoplasms were: P-388 leukemia, 137%; B-16 melanoma, 122%; Lieberman plasma cell tumor, greater than 85%; colon tumor 26, 150%; Ridgway osteogenic sarcoma, 85%. There were significant numbers of long-term survivors. Both DNA and RNA synthesis were strongly inhibited. The drug was resistant to biodegradation and was bound strongly to tissues; in monkeys the half-life for disappearance from serum was 6 days. Related hydrazones were synthesized, and structure-activity relationships are discussed. Two routes to ring-substituted anthracene-9,10-dicarboxaldehyde intermediates were developed. (Author abstract) (52 Refs)

48. AGENTS WITH POTENTIAL SPECIFICITY AGAINST MELANOTIC MELANOMA.

Lin AJ, Kelley JA, Breitman TR, Driscoll JS
Lab. Medicinal Chemistry and Biology, NCI, NIH, Bethesda, MD, 20205
J Med Chem; 25(5):501-505 1982

Agents were designed to exploit the high tyrosinase activity in melanotic melanoma relative to normal tissues. If specific tyrosinase activation of these agents occurred, the production of toxic metabolites in the melanoma cells would produce selective cell kill. Synthesis and antitumor activities of three new amino acids, (1a) [beta-[(p-hydroxyphenyl)amino]alanine hydrochloride], (1b) [Ndelta -(p-hydroxyphenyl)ornithine hydrochloride], and (1c) [Ndelta-(m-hydroxyphenyl)ornithine dihydrochloride], were described. Compounds 1a and 1b were approx two-fold more active against the B-16 melanotic melanoma than the amelanotic melanoma cell line in vitro. Compound 1b was approx two-fold more potent than compound 1a against either cell line and was eight-fold more potent than L-glutamic acid gamma-(4-hydroxyanilide), a natural product isolated from mushroom. No significant growth inhibitory activity was found for the m-hydroxy analogue 1c at 100 uM, the highest concentration tested. Similarly, compound 1b exhibited better activity against P-388 (ED50 = 9.5 x 10(-6) M) than 1a (ED50 = 3.2 x 10(-5) M) and was about 30-fold more potent than 1c. Against human epidermoid carcinoma of the nasopharynx (KB), these agents showed modest inhibitory activity with ED50 values in the range of 1.2 to 3 x 10(-4) M. No in vivo activity against P-388 and B-16 at doses up to 150-200 mg/kg was observed. The biological results suggest that a nonspecific oxidation rather than a specific tyrosinase activation is involved in the biological action of these new compounds. (Author abstract) (21 Refs)

49. CHEMOTHERAPEUTIC APPROACHES TO BRAIN TUMORS. EXPERIMENTAL OBSERVATIONS WITH DIANHYDROGALACTITOL AND DIBROMODULCITOL.

Levin VA, Wheeler KT
Dept. Neurological Surgery, Sch. Medicine, Univ. California, San Francisco, CA, 94143
Cancer Chemother Pharmacol; 8(1):125-131 1982

Effects of dianhydrogalactitol (DAG) on cell kill and division delay of 9L tumor cells in vitro, a comparison of in vitro and in vivo exposure doses, and evaluation of DAG and dibromodulcitol (DBD) in two drug combinations in intracerebral (IC) tumor models are described. The shape of the in vitro dose-response curves for 9L cells exposed to various concentrations of DAG for 1 hr or 24 hr was similar to that observed for most oncolytic agents. The Do and Dq for the 1-hr exposure were 4.6 ug/ml and 2.6 ug/ml, respectively; for the 24-hr exposures they were 0.21 ug/ml and 0.082 ug/ml. The appearance of colonies in the petri dishes was delayed to a greater extent as the survival of clonogenic cells decreased. This delay in the appearance of colonies was not caused by slower growth of the clonogenic survivors of the DAG treatment. The close correspondence between the log cell kill achieved after 1 hr or 24 hr at comparable in vitro DAG exposure doses, calculated by assuming no significant decrease in DAG concentration over a 24-hr exposure period, indicated that DAG had a very long half-life. The antitumor activity of DAG was minimal against the IC 9L gliosarcoma 26 models, but very effective against IC ependymoblastoma. The antitumor activity of DBD against IC glioma 26 was also minimal. When DAG or DBD was combined with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) to treat glioma 26, a substantial improvement in therapy occurred for the DAG-BCNU combination, but less improvement was evident for the DBD-BCNU combination. The DAG-BCNU therapy schemes were essentially as effective in treating IC glioma 26 as DAG alone was in treating IC ependymoblastoma. (12 Refs)

50. CURRENT DEVELOPMENT OF PODOPHYLLOTOXINS.

Canetta R, Hilgard P, Florentire S, Bedogni P, Lenaz L
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Cancer Chemother Pharmacol; 7(2/3):93-98 1982

Recent findings in studies of semisynthetic derivatives of the podophyllotoxins teniposide (VM26, Vumon) and etoposide (VP16-213, Vepesid) are reviewed. Studies include those of pharmaceutical formulation, stability, pharmacokinetics, single agent activity, therapeutic synergism, and combination chemotherapies. The most tolerated mode of administration is via a soft gelatin capsule containing etoposide in soln. Both drugs are active in chemotherapy of malignant lymphoma, small cell lung cancer, acute non-lymphoblastic leukemia, testicular cancer, choriocarcinoma, bladder cancer, and neuroblastoma. Due to low and predictable toxicity, podophyllotoxins may be administered synergistically with other drugs. The most promising results were obtained with the combination of cytosine arabinoside and teniposide and the combination of cisplatin and etoposide. Various combinations of cyclophosphamide, adriamycin, vincristine, and cisplatin, with podophyllotoxin for treatment of oat cell lung cancer are tabulated. Other combinations are discussed, including substitution for a vinca alkaloid in an established regimen, addition of one podophyllotoxin to an active combination, designing of new cross-resistant combinations, and cyclic sequential combination chemotherapy. (60 Refs)

51. SYNTHESIS AND PROPERTIES OF NEW IMIDAZOLE NITRODERIVATIVES.

Mokrushin VS, Selezneva IS, Pospelova TA, Usova VK, Malinskaia SM, Anoshina GM, Zubova TE, Pushkareva ZV
Ural Polytechnical Inst., Sverdlovsk, USSR
Khim Farm Zh; 16(3):303-307 1982

Synthesis of 10 o-nitrotriazene derivatives of imidazole is described. The antitumor activity of synthesized compounds was tested in cultured cells of Ehrlich's ascites carcinoma, Fisher's tumor, lymphoma NK/Ly, and sarcoma 37, as well as in random-bred mice bearing the transplanted adenocarcinoma 755, Lewis lung carcinoma, sarcoma 37, and sarcoma 180. Of ten compounds tested, only 5(4)-nitroimidazole-4-(5)-o-acetylhydroxamic acid provided a 54% inhibition of sarcoma 37. (7 Refs) (In RUS)

52. SYNTHESIS AND ANTITUMOR ACTIVITY OF ETHYL ETHER OF 4-(DI-(2,-CHLOROETHYL)AMINO)-L-PROLINE.

Koksharova TG, Rozin IuA, Sokolova VN, Barybin AS, Zubova TE, Pushkareva ZV, Lobova TG, Sof'ina ZP
S. M. Kirov Polytechnical Inst., Sverdlovsk, USSR
Khim Farm Zh; 16(3):284-287 1982

Antitumor activity of newly synthesized ethyl ether of 4-(di-(2,-chloroethyl)amino)-L-proline (compound Ia) was studied in BDF mice bearing leukemia L1210, leukemia P388, leukemia L5178Y, and melanoma B-16, in C57BL mice bearing leukemia La, adenocarcinoma Ca-755, and Lewis lung carcinoma, and in random-bred rats bearing Walker 256 carcinosarcoma. Compound Ia provided mild inhibition of leukemias L1210 and

F388, marked inhibition of leukemia L5178Y, and 70-100% inhibition of Ca-755. Compound Ia was ineffective against leukemia La, Lewis lung carcinoma, and melanoma B-16. Compound Ia penetrated the brain-blood barrier and inhibited the growth of intracerebrally transplanted Walker carcinosarcoma. (3 Refs) (In RUS)

53. SYNTHESIS AND ANTITUMOR ACTIVITY OF SELENO- AND THIO-PURINES COMPLEXED WITH CIS-DIAMMINOPLATINUM (II).

Maeda M, Abiko N, Sasaki T
Natl. Cancer Center Res. Inst., Tsukiji 5-Chome, Chuo-ku, Tokyo 104, Japan
J Pharmacobio Dyn; 5(2):81-87 1982

Complexes of cis-diamminoplatinum (II) (cis-DPT) with selenoguanine, thioguanine, 6-thioxanthine (TX), or 6-mercaptopurine were synthesized by the reaction of stoichiometric amounts of selenopurine or thiopurine with aquated cis-dichlorodiammineplatinum (II) in slightly acidic medium, and antitumor activity against L1210 cells in mice was studied. Nuclear magnetic resonance and infrared spectroscopic data were difficult to interpret due to technical problems, but UV spectral properties suggested that cis-DPT (II) chelates on the sulfur or on the selenium atom at position 6 and on the nitrogen at position 7 in the purine ring. The molar ratio of purines to diamminoplatinum in the complexes was 1:1. The complexes had a moderate antitumor activity and slightly higher toxicity than corresponding symmetric complexes used in earlier experiments, except for the cis-DPT-TX complex which showed no antitumor activity in all. TX alone showed no antitumor activity either. The purine moiety appears to be released slowly from the complex, which explains the reduced toxicity of the complexes compared to purines alone. (23 Refs)

54. EFFECTS OF SELECTED COMPOUNDS ON THE MCCALL RAT COLON ADENOCARCINOMA.

Sugiura K, Schmid F, Otter G, Stock CC
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Gan; 73(2):206-211 1982

Forty-seven substances were tested for antitumor activity against the McCall rat colon adenocarcinoma. The most effective compounds were mitomycin mitomycin C, 1,1',1'-phosphinothiolylidynetrisaziridine and adriamycin. Others less active were azaserine, N-(4-chlorophenyl)-N'-(1-methylethyl) imidodicarbonimidic diamide and 3,6-bis(5-chloro-2-piperidinyl)-2,5-piperazinedione. A number of standard anticancer drugs, 5-fluorouracil, arabinosylcytosine, methotrexate, bleomycin, daunomycin, 6-mercaptopurine, cis-dichlorodiammine platinum(II), cyclophosphamide and actinomycin D, were not effective under the test conditions and evaluation procedure used. Lentinan, though causing no initial inhibitions of growth, did cause some regression. Significant synergism in terms of regression was seen in combination therpy with mitomycin C and azaserine. (Author abstract) (7 Refs)

55. ELECTRON MICROSCOPIC STUDY OF THE EPITHELIAL CELLS OF THE VENTRAL LOBE OF RAT PROSTATE GLANDS FOLLOWING TREATMENT WITH PEPLOMYCIN SULFATE.

Okada K, Yamamoto T, Gon H, Kishimoto T
Dept. Urology, Nihon Univ. Sch. Medicine, Tokyo, Japan
Jpn J Antibiot; 34(8):1148-1157 1981

Peplomycin sulfate (NK631) was administered ip to 200-300 g male Wistar rats to study the effects of the drug on rat body wt and ultrastructure of the prostate tissues. The rats were divided into three groups - control group (5 rats), castrated (15), and NK631-treated (15). The castrated rats were sacrificed days 4, 7, or 14 after castration, and the NK631-treated rats were sacrificed days 4, 7, or 14 after initiation of daily treatment with NK631 (5 mg/kg/day). Body wt and the ratio of the rats' body wt and prostate wt (BW:PW) were measured during the experiment and at the time of sacrifice. BW:PW decreased to 8:1 on day 14 in the castrated rats. A slight decrease in the ratio was observed on day 14 in the NK631-treated rats; the ratio was significantly less than that of the control rats, but less change and atrophy was observed in the NK631-treated rats compared to the castrated rats. Cells in the ventral lobe of the prostate in the castrated rats showed loss of normal cytoplasmic configurations, atrophy of the rough endoplasmic reticulum (ret) and Golgi apparatus, and secondary lysosomes. Cells in the prostate glands of the NK631-treated rats showed marked vacuolization and degeneration of ret, disappearance of cytoplasmic matrix and nucleoplasm, and marked indentation of nuclear membrane. Because NK631 induced cytostatic changes in the ventral lobe of the rat prostates, potential application of NK631 to treatment of prostatic carcinoma was suggested. (18 Refs) (In JPN)

INTERFERON AND OTHER ANTIVIRALS

56. SERUM AND CEREBROSPINAL FLUID (CSF) PHARMACOKINETICS OF RECOMBINANT LEUCOCYTE A INTERFERON (IFLRA) IN MONKEYS (MEETING ABSTRACT)

Riccardi R, Kramer MJ, Trown PW, O'Neill D, Levine AS, Poplack DG

National Cancer Institute, Bethesda, MD, 20205

Proc Am Assoc Cancer Res; 23:799 1982

We investigated the serum and CSF pharmacokinetics of IFLrA following IM, IV and IT administration in rhesus monkeys. Animals with subcutaneously implanted reservoirs were utilized for these studies. Following IV and IM injections of 2.5 and 5x10(6) U/kg, serum samples were taken at 2, 5, 10, 15, 30, 45, and 60 mins, and 1.5, 2, 3, 5, 8 and 12 hrs. After IV administration at the two different doses, serum levels of about 2.5x10(4) U/ml and 6x10(4) U/ml were achieved at 2 mins and declined rapidly, with an alpha and beta half life of about 16 and 340 mins respectively. Following administration of identical doses of IM IFLrA, serum levels peaked at 4 hrs. In contrast to IV injection, serum IFLrA levels were sustained for approximately 6 hrs following IM administration. However, the area under the curve (AUC), a measure of the amount of drug present in the systemic circulation over time, was similar in both circumstances. Peak CSF levels following both IV and IM administration were below 0.05% of the peak serum levels. Following intraventricular administration of 1x10(6) U of IFLrA, CSF levels declined with a single half life of about 2 hrs. No major toxicity was observed following the three different routes of administration. Our data indicate that 1) although different peak levels of IFLrA were observed following IV or IM administration, the AUC were similar in each case; 2) only a fraction of circulating IFLrA penetrates into the CSF following parenteral administration; and 3) sustained CSF IFLrA levels can be achieved following intraventricular administration. (no Refs)

57. CHANGES IN DNA-POLYMERASE AND THYMIDINE KINASE ACTIVITY DURING INTERFERON TREATMENT.

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Biochem Biophys Res Commun; 105(4):1569-1576 1982

The effect of human interferon beta (IFN-beta) on the human glioma cell line, U-251 MG, was investigated. Exponentially growing cells treated with IFN exhibited a dose-dependent growth depression observed after 3 days, and an increase in the amount of cells in S phase. However, the activity of DNA polymerase was decreased to 30% of control levels at day 5 with 1,000 Units/ml of IFN-beta. This depression in enzyme activity may be explained by an inhibitory effect of IFN on the increase of enzyme activities induced by events in late G1 or early S, or by the induction of diffusable factors depressing enzyme activities. Starved cells were induced to cycle and DNA content was followed cytofluorometrically. S phase started approx 12 hr after addition of serum to synchronized cells and cells entered G2 at 21 hr. In contrast, IFN-treated cultures initiated S but accumulated in that phase. At the start of S phase, both DNA polymerase and thymidine kinase activity increased, although the rate of increase was markedly reduced by treatment with IFN. No inhibitory factor could be identified in the IFN treated cultures. It is probable that IFN has a direct effect on the induction of the studied enzyme activities, thus affecting virus replication. (18 Refs)

58. INHIBITORY EFFECTS OF LENTINAN ON THE TUMORIGENESIS OF ADENOVIRUS TYPE 12 IN MICE.

Hamada C, Aoki T, Nakanishi A, Hashimoto Y

Dept. Virology, Niigata Univ. Sch. Medicine, Niigatashi, Japan

Excerpta Med Int Congr Ser; 576:76-87 1981

The effect of Lentinan on human adenovirus type 12 (AD12)-induced tumor growth and normal spleen cell (NSC) activity was investigated in C3H/He mice, which develop tumors, and C57BL/6 mice, which are resistant to tumor development. Newborn mice were inoculated with 1 x 10(7) TCID50 (50% tissue culture infective dose) sc on their backs, and observed for tumor growth for 3 mo. NSC were assayed for natural killer (NK) activity by a 51Cr-release test. In C3H/H3 mice tumors started to develop at 40 days postinfection (pi) and were present in 15/20 (75%) animals at 90 days pi. Tumors did not develop in C57BL/6 mice during this period. In these mice cytotoxic activity began at 3 wk, peaked at 5 wk, and then declined until 10 wk. In the C3H/He mice no cytotoxic activity was noted. Treatment of C3H/He mice with a single dose of 10 mg/kg Lentinan ip gave good induction of cytotoxic NSC. Three successive doses (10 mg/kg each) of Lentinan at 1-day intervals were optimal for NSC induction, giving results comparable to those of C57BL/6 mice for 5 days after treatment. This same regimen gave the best tumor inhibition when injected at 14-18 days pi, and resulted in tumor incidence of 6/15 (40%), as compared to 11/14 (78.6%) in controls (p less than 0.05). These results indicate that NSC have a crucial role in preventing AD12 tumors in resistant mice. (14 Refs)

OTHER RELATED STUDIES

59. B16 MELANOMA CELL VARIANTS: IRREVERSIBLE INHIBITION OF GROWTH AND INDUCTION OF MORPHOLOGIC DIFFERENTIATION BY ANTHRACYCLINE ANTIBIOTICS.

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JNCI; 68(4):629-638 1982

The interaction of doxorubicin and N-trifluoroacetyladriamycin-14-valerate (AD32) with B16 melanoma cell variants that exhibit distinct metastatic properties was explored. The addition of the two drugs to cell monolayers at noncytolytic concentrations for 16 hr resulted in irreversible inhibition of proliferation of tumor cells and loss of their tumorigenicity after injection into inbred C57BL/6 mice. Cessation of melanoma cell proliferation was accompanied by cellular and nuclear hypertrophy and the development of axon-like processes. As assessed by drug-specific cytofluorescence, after 16-hr exposure of the cells to doxorubicin and AD32, the drugs were localized in the nuclei. Incubation of drug-treated cell monolayers for 6 additional days in drug-free culture medium led to the complete disappearance of nuclear stain. The highly metastatic B16-F10-B2 cell line was the most sensitive to the drugs' effects, whereas the other two malignant melanoma cell lines, although differing in their metastatic capabilities, exhibited similar sensitivities to the drugs' effects. Doxorubicin was notably more potent than AD32 in its growth inhibitory effect on the three tested melanoma cell variants. The possible mutagenic effect of anthracycline drugs on tumor cells was discussed. (Author abstract) (42 Refs)

60. ON THE MECHANISM OF HYDROGEN PEROXIDE-, SUPEROXIDE-, AND ULTRAVIOLET LIGHT-INDUCED DNA CLEAVAGES OF INACTIVE BLEOMYCIN-IRON(III) COMPLEX.

Sugiura Y, Suzuki T, Kuwahara J, Tanaka H

Faculty Pharmaceutical Sciences, Kyoto Univ., Kyoto 606, Japan

Biochem Biophys Res Commun; 105(4):1511-1518 1982

The reaction mechanism for H2O2-, KO2-, and UV-induced DNA cleavage of the inactive bleomycin-Fe(III)-OH-[(BLM)-FE(III)-OH-] complex was investigated. DNA cleavage activity was clearly produced by the addition of H2O2 or KO2 to the inactive complex. When H2O2 was added (1-20 milliMoles), the electron spin resonance (ESR) spectrum was dramatically changed. Addition of solid KO2 (0.05-0.5 mg) gave similar ESR results. These iron complexes converted back to the original BLM-FE(III)-OH- complex upon standing in air. UV-light irradiation toward the inactive BLM-Fe(III)-OH- complex induced DNA cleavage activity in a reproducible manner. Based on these results, a hypothetical mechanism for cyclic function of BLM-iron complex for DNA cleavage reaction is proposed: H202 probably contributes to the conversion from the inactive BLM-Fe(III)-OH- complex to the ative BLM-Fe(III)-O2H- complex, and UV light to the reduction of the BLM-Fe(III)-OH- complex to the BLM-Fe(II) complex. The positive effect of H2O2, KO2, and UV light on DNA cleavage by the inactive BLM-Fe(III)-OH- complex is highlighted, and the possible application of BLM-UV combination therapy for certain cutaneous cancers is mentioned. (20 Refs)

61. REPAIR OF DNA INTERSTRAND CROSSLINKS AFTER BUSULPHAN. A POSSIBLE MODE OF RESISTANCE.

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Cancer Chemother Pharmacol; 8(1):3-7 1982

The technique of alkaline elution was used to study the interaction between busulfan (BS) and the DNA of cells derived from the transplantable rodent Yoshida sarcoma. The findings were related to the in vitro cytotoxicity and chromosome aberrations (CHA) in the anaphase of cell lines resistant (YR) and sensitive (YS) to BS are discussed. The doses of BS producing 50% cell death were 7.5 and 54.5 ug/ml for YS and YR, respectively. BS (50 ug/ml) treatment in both cell lines caused a greater than two-fold depression in the mitotic index after 24 hr post-treatment incubation. A four-fold greater number of CHA could be observed in the YS than the YR line. Typical elution profiles in YS cells after a single 1-hr dose of BS (100 ug/ml) are presented. A small but reproducible proteinase-resistant retention was observed immediately after BS treatment, indicating the presence of DNA interstrand cross-links. As the dose of BS was increased, an increasing filter retention was observed, from which the number of cross-links per unit DNA could be assessed. The relationship between drug dose and the frequency of DNA interstrand cross-links is shown. A temporal study of DNA interstrand cross-linking after a single dose of BS (50 ug/ml; 1 hr) revealed a gradual increase in cross-linking over the first 4 hr, followed by a disappearance over 24 hr in the YR line. In the YS line, an increase in cross-linking over 4 hr and very little loss was observed 24 hr after drug removal. The time-course of cross-linking in both lines in terms of the relative retention is shown. (19 Refs)

62. EFFECTS OF METHOTREXATE ON RIBONUCLEOTIDE POOLS IN GROWING AND IN GROWTH-ARRESTED TUMOR CELLS AND ANTAGONISM BY RNA SYNTHESIS INHIBITORS.

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J Biol Chem; 257(8):4279-4284 1982

We examined the mechanism of ribonucleotide pool changes in methotrexate-treated Ehrlich ascites tumor cells in culture. In exponentially growing cells, methotrexate inhibited ATP and GTP formation and stimulated UTP and CTP formation by the de novo pathways. Over the following 4 hr ATP and GTP decreased and UTP and CTP increased. During this period RNA synthesis rates decreased by 30 to 40%. Inhibitors of nucleolar RNA synthesis (actinomycin D, doxorubicin, or cycloheximide), but not of DNA synthesis (cytosine arabinoside), prevented ATP and GTP depletion. These results suggest that ATP and GTP were depleted in methotrexate-treated cells because the shift-down of RNA synthesis occurred more slowly than the inhibition of ATP and GTP supply. UTP and CTP pools increased because of increased de novo synthesis and because of decreased consumption in RNA synthesis. Ribonucleoside triphosphates were increased and their syntheses by de novo pathways were inhibited in cells treated with RNA synthesis inhibitors. ATP decreased slightly and GTP remained unchanged in growth-arrested cells treated with methotrexate. In growth-arrested cells, de novo purine nucleotide synthesis was inhibited less and RNA synthesis rates were lower than in growing cells. (Author abstract) (45 Refs)

63. THERAPEUTIC EFFECT OF AN AROMATIC RETINOIC ACID ANALOG ON RATS WITH BLADDER CARCINOMA UPON ADMINISTRATION ALONE OR IN COMBINATION WITH MITOMYCIN C.

Fujita J, Miyakawa M, Tokuda H, Yoshida O
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Gan; 73(2):285-288 1982

An aromatic retinoic acid analog (Ro 10-9359) was given orally in combination with intraperitoneal administration of mitomycin C (MMC), in an attempt to reduce the toxicity and enhance the therapeutic effect. Male ACI/N rats were inoculated subcutaneously with BC50-TC cells, an established bladder carcinoma cell line of ACI/N rats. The chemotherapy was initiated at 16 days after the inoculation and continued for 4 wk thereafter. Tumor growth was significantly inhibited in the rats given 100 mg/kg/wk Ro 10-9359 or 0.3 mg/kg/twice a wk MMC. Neither additive nor synergistic effect was apparent when these two drugs were given simultaneously. No effect was seen when 0.1 mg/kg/twice a wk MMC was given alone or in combination with Ro 10-9359. MMC may suppress Ro 10-9359 activity directly or indirectly by affecting the responding cells. Therefore care should be taken when prescribing retinoids with MMC or possibly with other cytotoxic agents. (Author abstract) (22 Refs)

64. A POSSIBLE PARAMETER TO CLASSIFY IMMUNOMODULATORS.

Mizuno D, Hosokawa M, Ishida N, Herberman RB, Urushizaki I, Kumagai K
Teikyo Univ., Teikyo, Japan
Excerpta Med Int Congr Ser; 576:254-258 1981

On the basis of induction of LB in ddY mice after ip injection of various compounds, immunomodulators were classified into Type O, causing no increase (eg, levamisole, bestatin); Type 1, causing a rapid increase (eg, lipopolysaccharide, dextran sulfate, polyinosinic acid-polycytidylic acid); and Type 2, causing a slow increase (eg, Lentinan, TAK, PS-K, adriamycin). Studies against Ehrlich carcinoma suggest that the different types of compounds have synergistic antitumor activities. (1 Ref)

65. NONINTERCALATIVE DNA-BINDING ANTITUMOUR COMPOUNDS.

Baguley BC
Cancer Res. Lab., Univ. Auckland Medical Sch., Private Bag, Auckland, New Zealand
Mol Cell Biochem; 43(3):167-181 1982

A family of compounds which appear to bind reversibly to double stranded DNA without intercalation between DNA base pairs has been defined. Methods are described by which this non-intercalative binding can be characterized using ultraviolet spectrometry, fluorimetry with ethidium as a probe, viscometry and other hydrodynamic techniques, circular dichroism and nuclear magnetic resonance spectrometry. antibiotics which fall into this family include the antibiotics distamycin A, netropsin, mithramycin, chromomycin and olivomycin. Synthetic antitumor agents include diarylamidines such as berenil, phthalanilides, aromatic bisguanylhydrazones and bisquaternary ammonium heterocycles. A survey has been made of the general requirements of this family of compounds for DNA binding and biological activity. Binding of drugs to the minor groove of the DNA double helix appears to be the most likely mechanism for the antitumor action of these compounds (Author abstract) (91 Refs)

66. IN VIVO INACTIVATION BY ACIVICIN OF CARBAMOYL-PHOSPHATE SYNTHETASE II IN RAT HEPATOMA.

Aoki T, Sebolt J, Weber G
(c/o Weber) Lab. Experimental Oncology, Indiana Univ. Sch. Medicine, Indianpolis, IN, 46223
Biochem Pharmacol; 31(6):927-932 1982

The antitumor drug acivicin, L-(alphaS,5S)-alpha-amino-3-chloro-4,5-dihydro-5 isoxazoleacetic acid, in vivo irreversibly inactivated carbamoyl-phosphate synthetase II (glutamine-dependent; EC 6.3.5.5), the first and rate-limiting enzyme of de novo pyrimidine nucleotide biosynthesis, in transplantable rat hepatoma and host liver. With two injections of 0.5 mg acivicin per 100 g body wt to one group and two injections of 5 mg to another group, enzyme activity decreased to 20 and 1% in hepatoma and to 99 and 31% in liver, respectively. Aspartate carbamoyltransferase (EC 2.1.3.2) activity was not affected. Acivicin in vitro selectively inactivated glutamine-dependent activity of the synthetase II from the hepatoma and liver, with an inactivation constant (Kinact) of 90 uM and a min inactivation halftime (T) of 0.7 min. The inactivation velocity with 10 uM acivicin was 5.0-fold stimulated by 2 mM MgATP and 18.4-fold by 2 mM MgATP plus 16.7 mM bicarbonate. MgATP at 0.5 mM caused half-max stimulation of the inactivation velocity. Under in vitro conditions, L-glutamine (1 mM) protected the enzyme from inactivation by 10 uM acivicin. The synthetase activity was protected in vitro by 6 mM concentrations of glycine (84%), L-glutamate (59%) and L-aspartate (51%) and by 0.5 mM UTP (35%) from inactivation by 20 uM acivicin. The results are compatible with the suggestion that acivicin is an active site-directed affinity analog of L-glutamine. (Author abstract) (23 Refs)

67. EFFECT OF ALCOHOL ON TUMOR FOLATE SUPPLY.

Steinberg SE, Campbell CL, Hillman RS
Dept. Medicine, Hennepin County Medical Center, 701 Park Ave., Minneapolis, MN, 55415
Biochem Pharmacol; 31(7):1461-1463 1982

Effects of alcohol on peripheral tissue folate supply were studied in a new animal model where multiple sc fibrosarcoma implants permit kinetic measurements of folate transport by serial sampling of the tumor nodules. The amount of polyglutamyl folate present was calculated as the percentage of total labeled folate in the tissue. Results showed that the known toxic effect of alcohol on the enterohepatic cycle is associated with a major reduction in folate supply to a peripheral tissue (tumor), together with an increased accumulation of tumor polyglutamyl folate similar to that reported for the hepatocyte. (14 Refs)

68. PARTICIPATION OF POLY(ADP-RIBOSYL)ATION IN THE DEPRESSION OF RNA SYNTHESIS CAUSED BY TREATMENT OF MOUSE LYMPHOMA CELLS WITH METHYLNITROSOUREA.

Taniguchi T, Agemori M, Kameshita I, Nishikimi M, Shizuta Y
Dept. Medical Chemistry, Kochi Medical Sch., Kochi 781-51, Japan
J Biol Chem; 257(8):4027-4030 1982

When mouse lymphoma cells (L-1210) are treated with methylnitrosourea, a DNA-damaging agent, polyadenosine diphosphoribose (poly(ADP-ribose)) synthetase activity increases five to eight-fold in 2-3 hr, while RNA polymerase activity remains constant for an initial 2 hr and then gradually decreases to 25-30% of the control level in 5 hr. Both alpha-amanitin-sensitive and -resistant RNA polymerase activities are depressed to the same degree by the treatment with methylnitrosourea. The depression in RNA synthesis is virtually prevented when the treated cells are cultured in the presence of 3-aminobenzamide, a specific inhibitor of poly(ADP-ribose) synthetase. Analyses of the RNA extracted from the cells labeled with [3H]uridine by agarose gel electrophoresis and by poly(U)-Sepharose column chromatography show that the contents of ribosomal precursor RNA and poly(A)-containing RNA are both low in the methylnitrosourea-treated cells as compared with those in the untreated cells and that the reduction in the contents of these kinds of RNA is almost completely prevented by the addition of 3-aminobenzamide to the culture medium. These results suggest that the enhancement of poly(ADP-ribosyl)ation causes the decrease in both synthesis of ribosomal RNA and messenger RNA. (Author abstract) (36 Refs)

69. EFFECT OF RETINOIC ACID PRETREATMENT ON 12-O-TETRADECANOYLPHORBOL-13-ACETATE-INDUCED CELL POPULATION KINETICS AND POLYAMINE BIOSYNTHESIS IN HAIRLESS MOUSE EPIDERMIS.

Astrup EG, Paulsen JE
Inst. Pathology, Univ. Oslo, Rikshospitalet, Natl. Hosp., Oslo 1, Norway
Carcinogenesis; 3(3):313-320 1982

A single topical application of 17 nmol 12-O-tetradecanoylphorbol-13-acetate (TPA) to the skin of hairless mice induces characteristic transient alterations in the epidermal cell turnover and maturation (0-96 hr), associated in time with characteristic changes in the activities of L-ornithine carboxy-lyase (EC 4.1.1.17) (ODC) and S-adenosyl-L-methionine carboxy-lyase (EC 4.1.1.50) (SAM-D) and in the accumulation of polyamines. The effects on these responses of local pretreatment of the skin with retinoic acid 1 hr prior to TPA were investigated at selected time points. Retinoic acid inhibited the TPA-induced ODC activity and the ensuing accumulation of putrescine, but did not alter the TPA-induced SAM-D activity or the molar ratio of spermidine/spermine. This pretreatment also decreased the number of dividing basal cells in the first TPA-induced synchronized wave of proliferating cells. However, during the subsequent period of proliferation, the number of dividing cells in the retinoic acid pretreated group was comparatively increased. Hence, at four dose levels of retinoic acid (0.17, 1.70, 17.0 and 170 nmol), which all inhibited the TPA-induced ODC effectively, there was no change in the total number of basal cells that divided during 16-48 hr after TPA-application. The theory is put forward that retinoic acid might exert its antitumorigenic effect during tumor promotion with TPA by interfering with the rate and/or quality of epidermal cell maturation, rather than by inhibiting cell proliferation. (Author abstract) (62 Refs)

70. PYRIDOXINE RESISTANCE IN A RAT HEPATOMA CELL LINE.

DiSorbo DM, Paavola LG, Litwack G
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Cancer Res; 42(6):2362-2370 1982

The natural vitamin, pyridoxine, in the millimolar range is toxic to cultured rat hepatoma cells. A pyridoxine-resistant Fu5-5 rat hepatoma cell line was established by a stepwise increase in the concentration of pyridoxine in the medium. The newly established cell line, referred to as clone 10 (Cl.10), is resistant to killing by pyridoxine in concentrations up to 5 mM. Saturation kinetics for the uptake of [3H]pyridoxine into Fu5-5 and Cl.10 cells revealed that Fu5-5 cells take up 10x more [3H]pyridoxine than do Cl.10 cells. Whereas the Vmax value for the uptake of [3H]pyridoxine was the same for both cell lines, the apparent Km for the Cl.10 cells was 12.5 uM compared to 0.71 uM for the Fu5-5 cells. However, intracellular levels of pyridoxal 5'-phosphate were 69% higher in Cl.10 cells than in the parental line. The resistant line is neither a permeability mutant nor deficient in pyridoxal kinase. Cl10 cells contain 37% more adenosine 5'-phosphate than do Fu5-5 cells and have a mitochondrial volume that is 50% greater than that of the parental line. In the absence of pyridoxine in the medium, Cl.10 cells revert to parental type with respect to pyridoxine uptake but not with respect to resistance to killing. They also maintain an enlarged mitochondrial volume. Thus, increased mitochondrial volume may be related to the development of resistance to high levels of pyridoxine. (Author abstract) (21 Refs)

71. MODULATION OF 5-FU METABOLISM IN HUMAN MCF-7 BREAST CARCINOMA CELLS.

Major PP, Egan EM, Sargent L, Kufe DW
(c/o Kufe) Div. Pharmacology, Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA, 02115
Cancer Chemother Pharmacol; 8(1):87-91 1982

A previously reported relationship between the incorporation of 5-fluorouracil (5-FU) into total cellular RNA and loss of clonogenic survival in the human MCF-7 breast carcinoma cell line was studied in cells exposed to 5-FU and modulating agents such as N-(phosphonacetyl)-L-aspartate (PALA), methotrexate (MTX), and 6-methylmercaptopurine riboside (MMPR). Cells were grown in log phase and PALA (0.01, 0.10, and 1.0 mg/ml) and MTX or MMPR (concentrations of 10(-5)-10(-7) M) were added. Incorporation of 3H-FU and 32P into MCF-7 nucleic acids was measured, intracellular phosphoribosylpyrophosphate (PRPP) was determined, and clonogenic survival of MCF-7 cells was examined. Intracellular levels of PRPP were increased in the cells with the addition of PALA, MTX, and MMPR, while little if any significant increase in the absolute amount of FU incorporated into RNA was observed. The combination of PALA/MMPR resulted in the greatest absolute increases in formation of (5-FU)RNA (almost 2x control values). However, since PALA, MTX, and MMPR inhibit RNA synthesis, the absolute amount of 5-FU incorporated would not reflect the frequency of 5-FU substitution for uracil. In the presence of the modulating agents, the [3H]FU/32P ratio correlated better with loss of MCF-7 clonogenic survival than did the absolute amount of 5-FU incorporated in RNA. The [3H]FU/32P ratio may be useful for monitoring effects of other modulating agents on the metabolism of 5-FU. The relationship between (5-FU)RNA formation and loss of clonogenic survival should be corrected for the amount of newly synthesized RNA when 5-FU is combined with modulating agents that alter rates of RNA synthesis. (12 Refs)

72. COMPARISON OF IN VITRO AND IN VIVO EFFECTS OF THYMIDINE ON L1210 LEUKEMIA IN MICE.

Zaharko DS, Ramonas LM
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JNCI; 68(5):875-880 1982

Previous investigators have shown that L1210 leukemia in vitro growth can be inhibited by thymidine (dThd) by exposure for 24 hr to dThd concentrations as low as 0.1 mM. These experiments were conducted in an attempt to determine why dThd, although effective as a cytostatic agent against L1210 in vitro, is ineffective against L1210 in (BALB/c x DBA/2)F1 (CD2F1) mice. Systematic variations of dThd concentration and exposure times were examined in both a growth-inhibition assay and a soft agar cloning assay in vitro. The growth of cells exposed to 0.1-1.0 mM dThd for 15 hr was inhibited dramatically during exposure, but growth recovered to control rate rapidly when dTd was washed off the cells. With 96 hr of exposure to 1.0 mM dThd, growth rate did not return to control rate up to 120 hr after washing. Cloning efficiency was reduced to less than 1% of control by prior 96-hr exposure of L1210 cells to more than 0.5 mM dThd. Concentrations of deoxycytidine (dCyd) of 1.0 uM partially reversed cytotoxicity caused by dThd greater than 0.1 mM, and 10 uM dCyd completely reversed this cytotoxicity. In vivo plasma dThd concentrations during ip injections of 3,600 mg dThd/kg body wt every 8 hr for 4 days (approx lethal dose for 10% of animals treated) ranged from 10 to 0.1 mM, but these concentrations were ineffective in prolonging survival time of L1210-bearing mice. Plasma concentrations of dCyd prior to dThd exposure were less than 1.0 uM. Following injection of dThd (3,600 mg/kg body wt), plasma dCyd was 2.8 +-0.5 uM (normal mice) and 6.1 +-0.5 uM (L1210-bearing mice). Thus the rise of dCyd in plasma following dThd administration in vivo prevented the cytotoxicity of dThd seen in vitro from being manifested in vivo in CD2F1 mice. (Author abstract) (24 Refs)

73. DIETARY PHENYLALANINE/TYROSINE DETERMINES THE ANTITUMOR RESPONSE TO CARBIDOPA/LEVODOPA METHYL ESTER IN B-16 MELANOMA (MEETING ABSTRACT)

Meadows GG, Peirson HF

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Fed Proc; 41(3):280 1982

Dietary intake of phenylalanine (phe)/tyrosine (tyr) affects the survival of B6D2F1 mice bearing ip and sc B-16 melanoma and determines the antitumor effectiveness of Carbidopa (CD)/Levodopa methyl ester (LDME) chemotherapy. Tumor bearing mice maintained on a commerical diet (LabBlox) containing 24% protein, 1.09% phe and 0.64% tyr, or an 11.8% protein equivalent crystalline amino acid diet contining 2.00% phe and 1.00% tyr exhibit little increase in survival when treated with 100 mg/kg CD and 1000 mg/kg LDME daily for 15 days after tumor transplant. Mice maintained on an 11.8% diet containing 0.6% phe and 0.3% tyr and similarly treated with CD/LDME show a 35% (ip) and a 23% (sc) increase in survival. A diet equivalent to 23.2% protein and also containing 0.6% phe and 0.3% tyr does not alter the chemotherapeutic response to CD/LDME. An 11.8% diet containing 0.08% phe and 0.04% tyr inhibits growth of B-16 melanoma and increases survival of tumor bearing mice by 30% (ip) and 28% (sc) respectively; survival increases to 78% (ip) and 73% (sc) in CD/LDME treated mice indicating a diet-drug synergism. (no Refs)

74. E-17ALPHA-[125I]IODOVINYLESTRADIOL: AN ESTROGEN-RECEPTOR-SEEKING RADIOPHARMACEUTICAL.

Hanson RN, Seitz DE, Botarro JC
Dept. Medicinal Chemistry, Coll. Pharmacy and Allied Health Professions, Northeastern Univ., Boston, MA, 02115
J Nucl Med; 23(5):431-436 1982

Through the use of radioiododestannylation, the specifically labeled E-17alpha-[125I]iodovinylestradiol [(I-125)VE2] was synthesized rapidly and in high yield from the stable precursor E-17alpha-tributylstannylvinylestradiol (SnVE2), and its biodistribution was determined in immature female rats. The agent accumulated in the uterus, achieving a peak uptake of 0.465% ID-kg/g at 2 hr. Uterus-to-blood ratios of 19 and 16 occurred at 1 and 2 hr, respectively, declining to 7 by 4 hr after injection. The uptake of (I-125)VE2 by the uterus at 2 hr was reduced 58-65% by pretreatment of the immature rats with estradiol (5 ug) or tamoxifen (100 ug), and compared with 16alpha[125I]iodoestradiol, (I-125)VE2 showed greater uterine uptake and similar uterus-to-blood ratios. The ease of preparation of the radioligand represents an advantage over the synthetic procedures for other estrogen-receptor-seeking agents. (Author abstract) (26 Refs)

75. MECHANISM OF ACTION OF ANTITUMOR 3-(2-HALOETHYL)ARYLTRIAZENES ON DEOXYRIBONUCLEIC ACID.

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Dept. Chemistry, Univ. Alberta, Edmonton T6G 2G2, Alberta, Canada
Biochem Pharmacol; 31(7):1257-1266 1982

A series of novel 3-(2-haloethyl)aryltriazenes, many of which exhibit marked antileukemic activity in animal test neoplasms, react readily with DNA under physiological conditions. With regard to a single strand scission (SSS), in contrast to the related 2-haloethylnitrosoureas which exhibit both Type I and Type II SSS (single strand scission) of DNA, the triazenes appear to react via Type II SSS of DNA by base alkylation followed by depurination or depyrimidination and subsequent hydrolysis of the apurinic site. The latter reaction was confirmed using apurinic site-specific endonuclease VI. A 3-(2-chloroethyl)aryltriazene readily degraded poly A by phosphate alkylation at a rate much faster than given by comparable nitrosoureas. Overall, the triazenes showed a preference for reaction at the more acidic phosphate sites in the DNA owing to their unique acid-promoted decomposition. This may, in part, account for the lack of detection of DNA interstrand cross-links and indicates a fundamentally different mechanism of action of the 3-(2-haloethyl)triazenes from the 2-haloethylnitrosoureas. (Author abstract) (40 Refs)

76. GENETIC EFFECTS OF SOME PLATINUM CO-ORDINATION COMPLEXES ON E. COLI DNA AS REVEALED BY TRANSFORMATION STUDIES.

Hoekstra WP, Daemen CA, Otto ER

Dept. Molecular Cell Biology, State Univ. Utrecht, Padualaan 8, Utrecht 3584 CH, The Netherlands

Mutat Res; 94(1):53-62 1982

The genetic effects on Escherichia coli DNA of cis-diamminedichloroplatinum(II) (cisPt2), of its trans-isomer trans-PT2, and of cis-Pt(2.2-dimethyl-1,3-diaminopropane)Cl4 (cisPt4) are reported. Genetic analysis of transformants obtained with DNA treated by the various platinum complexes indicated that DNA lesions induced by cisPt2 and cisPt4 markedly influence genetic processing in recipient cells. No genetic effects were observed when trans-Pt2 was applied in similar concentrations. CisPt2 lesions appear to provide a stimulus for crossover events, while cisPt4 lesions lead to loss of linkage of genetic information in the donor DNA. The genetic effects of cisPt2 lesions in DNA were more pronounced in a uvrB recipient mutant than in a wild-type recipient, indicating that there is uptake of Pt-DNA and partial repair of Pt-induced lesions by the cellular excision repair system. The observation that transPt2 showed no effect when applied in similar concentrations at which cisPt2 gave significant effects may have relevance in terms of their differing efficacies as anti-neoplastic agents. (26 Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/126

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Experimental Therapeutics, Toxicology, Pharmacology

SERIES CB20 No. 82/10

OCTOBER, 1982

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ANTITUMOR AGENT EFFICACY IN VIVO

1. ANTITUMOR ACTIVITY OF A NEW ANTITUMOR ANTIBIOTIC, STUBOMYCIN.

Komiyama K, Edanami KI, Yamamoto H, Umezawa I
Kitasato Inst., Shirokane, Minato-ku, Tokyo, Japan
J Antibiot (Tokyo); 35(6):703-706 1982

The antitumor activity of a new antibiotic, stubomycin, against various murine tumors was studied. Stubomycin showed antitumor activity against Sarcoma 180, IMC-carcinoma and Meth-A tumor. In particular, all of the mice inoculated ip with IMC-carcinoma were cured when they were given nine successive injections of stubomycin. Stubomycin also showed remarkable antitumor effects against Sarcoma 180 and Ehrlich ascites carcinoma when administered concomitantly with bleomycin. (Author abstract) (9 Refs)

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HE 20.3173/2:

2. STUDIES ON THE EFFECT OF HIGH-DOSE METHOTREXATE-CITROVORUM FACTOR TREATMENT FOR 89SR INDUCED OSTEOSARCOMA IN MICE.

Nakamura T

Dept. Orthopedic Surgery, Sch. Medicine, Kanazawa Univ., Kanazawa, Japan

Nippon Seikeigeka Gakkai Zasshi; 56(2):149-161 1982

We treated mice with 39Sr induced osteosarcoma with HD MTX (high-dose methotrexate) and CF (rescue by citrovorum factor), and observed the results of MTX administration. MTX and CF constantly injected through their tail veins at intervals of 6, 24 hr, respectively. The amount of MTX administered ranged from 60 mg/kg to 2,000 mg/kg, while CF administered totalled 200 mg/kg. To determine their antitumor efficacy, we adopted 3H-thymidine based labeling index and mitotic index as well as microautoradiography, and observed how the tumor proliferation had been prohibited. The anti-tumor efficacy was significant when 500 mg/kg of MTX was administered. There was no significant increase in anti-tumor efficacy even after 1,000, 2,000 mg/kg of MTX had been administered. Rather, the tumor was tending to be healed as time passed by after administration of MTX being 500 mg/kg. Then we administered 500 mg/kg of MTX and 200 mg/kg of CF twice at intervals of 6 days. After we had administered MTX in combination with CF, we started observing the changing condition of the tumor. As a result, we recognized their significant anti-tumor efficacy. The tumor did not show any indication of serious growth. In view of the above, we concluded that it would be more effective to administer repeatedly an optimum dose of MTX and CF than to administer an ultra-high dose of MTX and CF. (Author abstract) (21 Refs) (In JPN)

3. GROWTH INHIBITION OF A PROSTATE TUMOR BY ALPHA-DIFLUOROMETHYLORNITHINE AND BY CYCLOPHOSPHAMIDE.

Heston WD, Kadmon D, Fair WR

Dept. Surgery, Washington Univ. Sch. Medicine, St. Louis, MO, 63110

Cancer Lett; 16(1):71-79 1982

The effect of difluoromethylornithine (DFMO) on the R3327MAT-Lu prostate-derived rodent tumor maintained in vivo was compared to that of cyclophosphamide (CP), which had already been shown to be effective in this model tumor system. R3327MAT-Lu ornithine decarboxylase (ODC) activity was found to be as sensitive to inhibition by in vivo DFMO administration as the normal prostatic enzyme. CP showed the most potent inhibition of growth of tumor cells. The combination of DFMO and CP was less inhibitory to tumor volume increase than CP alone. This antagonistic effect was significant by day 19 and remained so thereafter. Toxic effects on the host appeared additive. DFMO and CP reduced tumor wet wt by 30% and 99%, respectively. RNA/DNA was statistically different when CP-treated, but not DFMO-treated, animals were compared to controls. 3H-Thymidine incorporation was significantly decreased in both DFMO (32%) and CP (42%) groups. DFMO inhibited ODC activity by 98%, while no significant inhibition of ODC was observed between CP-treated animals and controls. Both the DFMO and CP groups exhibited significantly fewer lung metastases than the control group. In the control group all animals had lung metastases, compared to 91% in DFMO and 17% in CP-treated animals. (19 Refs)

4. EFFECT OF CYCLOPHOSPHAMIDE ON DEVELOPMENT OF RETICULUM CELL SARCOMA IN SJL/J MICE.

Crispens CG

Dept. Biology, Univ. Alabama in Birmingham, University Station, Birmingham, AL, 35294

Experientia; 38(5):624-626 1982

Studies to determine the effect of cyclophosphamide (CY) on the development of reticulum cell sarcoma (RCS) in SJL/J mice indicated a dependence on the duration of the test period. Age also appeared a factor of importance. Thus, a comparison of tumor incidences at 52 wk of age showed maximal inhibition when CY was administered at 40 wk, minimal inhibition when the drug was given at 30 wk, and intermediate inhibition when treatment was initiated at 10 and 20 wk. Consistent with these findings, long-term treatment of 40-wk-old SJL/J mice with low doses of CY resulted in an increase in the mean survival time and in a reduction in the incidence of RCS. (Author abstract) (17 Refs)

5. FUNDAMENTAL MODEL EXPERIMENT FOR CHEMOTHERAPY OF OSTEOSARCOMA USING TRANSPLANTABLE TUMOR.

Endo F, Takada N, Hodaka E, Tanaka N

Dept. Orthopedics, Chiba Cancer Center Hosp., Chiba, Japan

Nippon Seikeigeka Gakkai Zasshi; 55(10):1507-1508 1981

A multiple drug combination therapy using adriamycin (ADM, 2.5 mg/kg), vincristine (VCR, 0.5 mg/kg), high dose of methotrexate (MTX, 500 mg/kg), and cyclophosphamide (EDX, 50 mg/kg) markedly inhibited lung metastases of spontaneously occurring tumors in C3H mice. Administration of EDX alone or of the drug combination, ADM, VCR, MTX, and EDX, markedly reduced the tumor volume of human chondroblastic osteosarcoma. (no Refs) (In JPN)

6. EFFECT OF HIGH DOSE METHOTREXATE-CITROVORUM FACTOR TREATMENT FOR SR89 INDUCED OSTEOSARCOMA IN MICE.

Nakamura T, Tomita K, Munehiro T, Shimizu T, Yamada Y, Ciba H, Hayashi M, Nomura S

Dept. Orthopedics, Kanasawa Univ., Kanazawa, Ishikawa, Japan

Nippon Seikeigeka Gakkai Zasshi; 55(10):1505-1507 1981

To maintain a constant level of methotrexate (MTX) in the blood, MTX was given continuously through the tail vein for 6 hr to mice carrying Sr89-induced mouse osteosarcoma, and 3 hr later citrovorum factor (CF) was given continuously for 24 hr. For humans, serum MTX concentration reaches 10(-4) mol/liter for MTX doses of 175 mg/kg or 350 mg/kg. To reach the same serum MTX concentration in mice, a dose of more than 500 mg/kg was needed. At a dose of 500 mg/kg given through the tail vein, MTX blocked the incorporation of H3-thymidine (H3-TdR) into the tumor cells, (determined by microautoradiography). From these results, the dose 500 mg/kg was selected, and the time course changes of H3-TdR uptake were measured. In about a wk, the uptake of H3-TdR by the small intestine and bone marrow recovered back to the pretreatment level, whereas the uptake by tumors was below 40% of the pretreatment level. Histological changes and suppression of cell increase were not seen either, suggesting ineffective antitumor effect. When MTX at 500 mg/kg was given twice at an interval of 6 days, uptake of H3-TdR by tumors was no longer seen. A clear suppression of cell division and a significant lowering of mitotic changes compared to control (dose of 1 x 1,000 mg/kg) were noted. Apparently repeated MTX administration is more effective than a 1x-large dose treatment. (no Refs) (In JPN)

7. METABOLISM AND THERAPEUTIC EFFICACY OF 9-BETA-D-ARABINOFURANOSYL-2-FLUOROADENINE AGAINST MURINE LEUKEMIA P388.

Avramis VI, Plunkett W
(c/o Plunkett) Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Res; 42(7):2587-2591 1982

The biochemical basis for the differential therapeutic activity of equally toxic doses of 9-beta-D-arabinofuranosyl-2-fluoroadenine (F-ara-A) administered on two schedules to tumor-bearing mice has been studied. A single dose (234 mg/kg) of F-ara-A in solution decreased the number of P388 leukemia cells by greater than 10(3), whereas a multiple-dose regimen (41 mg/kg every day for 5 days) of equal toxicity to the host was ineffective at reducing the tumor burden. No antitumor activity was seen when an equal dose of the relatively insoluble F-ara-A was injected as a suspension. The 5'-triphosphate of F-ara-A accumulated in P388 cells in levels proportional to the dose of the nucleoside and disappeared from these cells at an exponential rate with a half-life of 2.9 hr, which was independent of the cellular concentration of the nucleotide. The extent and duration of the inhibition of DNA synthesis of P388 cells was dependent on the dose of F-ara-A, but the rates of recovery were similar and in proportion to the cellular concentration of the analog triphosphate. The extent of the inhibition of DNA synthesis in host bone marrow and intestinal mucosa was also related to the dose of F-ara-A, but the recovery of these tissues proceeded to similar, incomplete levels (less than 60% of initial) 24 hr after F-ara-A injection of either 41 or 234 mg/kg. These results suggest that the equal toxicity of the two regimens of F-ara-A may be attributed to the similar extent of inhibition of host-tissue DNA synthesis evoked by each. In contrast, the greater extent and longer duration of inhibition of P388 cell DNA synthesis caused by the single dose of F-ara-A was responsible for its superior therapeutic activity. Measurements of F-ara-A triphosphate concentrations and the DNA-synthetic capacity of tumor and host tissues are determinants of the action of F-ara-A and may be used to predict optimal therapeutic dose schedules. (Author abstract) (23 Refs)

ANTITUMOR AGENT EFFICACY IN VITRO

8. DEVELOPMENT OF NECROSES, VIRUS ACTIVATION AND GIANT CELL FORMATION AFTER TREATMENT OF EHRLICH ASCITES TUMOR WITH METALLOCENE DICHLORIDES.

Kopf-Maier P
Institut Anatomie, Freien Universitat Berlin, Konigin-Luise-Strasse 15, D-1000 Berlin 33, W. Germany
J Cancer Res Clin Oncol; 103(2):145-164 1982

Light-microscopic and ultrastructural alteration patterns are investigated after in vivo treatment of EAT with the cytostatic agents vanadocene dichloride (VDC) and titanocene dichloride (TDC). Both substances induce mitotic aberrations, eg, pyknotic metaphases, lagging chromosomes during anaphase, and multipolar mitotic figures. The appearance of mononucleate and, occasionally, multinucleate giant cells is observed mainly 48-96 hr at. The first observable ultrastructural changes are seen within the nucleus and consist of chromatin condensation and the enlargement of the nuclear surface. Thereafter, VDC induces morphological signs of unbalanced cellular growth, whereas TDC and cis-diamminedichloroplatinum (II) cause the development of necroses of the tumor cells, the phagocytosis of the damaged cells by macrophages, and, in consequence, complete tumor regression. Some hours after application of TDC, the formation of type-A-virus particles can be recognized. It is supposed that the apparent virus induction acts as a fortifying factor in the course of tumor inhibition by TDC. (Author abstract) (27 Refs)

9. TOXICITY OF LIPOSOMAL N-ACYL DAUNORUBICINS TO L929 CELLS IN CULTURE.

Bard DR, Knight CG, Page-Thomas DP
Strangeways Lab., Worts' Causeway, Cambridge CB1 4RN, England
Br J Cancer; 45(5):783-785 1982

Toxicity of N-acyl derivatives of daunorubicin (DNR) incorporated into dimyristoylphosphatidylcholine liposomes was determined for the murine areolar-tissue-derived cell line L929. Dose response curves showed that liposomes containing 10 mole % N-acyl DNR are less cytotoxic to L929 that free DNR. The mode of action of N-acyl DNR is discussed. (14 Refs)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

10. PROSTAGLANDIN E AUGMENTS THE EFFECT OF CHEMOTHERAPY ON B-16 MELANOMA IN VIVO.

Hofer D, Dubitsky A, Marti J, Santoro MG, Reilly P, Jaffe BM
(c/o Jaffe) Dept. Surgery, State Univ. New York Downstate Medical Center, Box 40, 450 Clarkson Ave., Brooklyn, NY, 11203
J Surg Res; 32(6):555-562 1982

The effectiveness of six chemotherapeutic agents (adriamycin, dopamine, 5-fluorouracil, nitrogen mustard, thioTEPA, and vincristine) on B-16 melanoma growth in vivo was compared with the effects of 16,16-dimethyl-PGE2-methyl ester, a long-acting synthetic analog of PGE2 (di-M-PGE2) and of chemotherapy plus di-M-PGE2. Although all the drugs were effective in slowing growth (adriamycin, dopamine, and 5-FU) or decreasing tumor size from baseline values (nitrogen mustard, thioTEPA, and vincristine), the addition of di-M-PGE2 augmented the growth inhibitory effects of each. Changes in tumor diameters were associated with similar changes in tumor cell numbers. In addition, the combinations of di-M-PGE2 plus nitrogen mustard and vincristine decreased the plating efficiency in a clonogenic assay to a greater extent than did either di-M-PGE2 or the cytotoxic drugs alone. Finally, this augmentation was not associated with systemic toxicity or changes in leukocyte count. (Author abstract) (16 Refs)

11. AUGMENTATION OF THE INTRACELLULAR LEVELS OF POLYGLUTAMYL DERIVATIVES OF METHOTREXATE BY VINCRISTINE AND PROBENECID IN EHRLICH ASCITES TUMOR CELLS.

Fry DW, Yalowich JC, Goldman ID
(c/o Goldman) Dept. Medicine, Medical Coll. Virginia, Richmond, VA, 23298
Cancer Res; 42(7):2532-2536 1982

The intracellular accumulation of poly-gamma-glutamyl derivatives of methotrexate was evaluated in the presence of vincristine or probenecid (agents which raise the intracellular level of free methotrexate) in Ehrlich ascites tumor cells. The results show that both intracellular methotrexate and its metabolites are increased by these agents and that, in the presence of L-glutamine, polyglutamate derivatives are increased by a higher percentage than is methotrexate. From 1 to 50 uM vincristine increased the levels of polyglutamate derivatives from 25 to over 300%, whereas methotrexate was raised from 25 to 80%. Similarly, 50 to 200 uM probenecid increased methotrexate polyglutamate derivatives from 31 to 88%, whereas methotrexate was raised from 0 to 30%. A determination of the bound fraction of drug indicated that the proportion of dihydrofolate reductase bound with methotrexate polyglutamates increased in the presence of these agents. Efflux studies showed that over 90% of the large pools of intracellular methotrexate polyglutamates produced by these agents was retained for at least 1 hr in the absence of extracellular methotrexate, whereas the majority of intracellular methotrexate exited the cell. These studies (a) indicate that vincristine and probenecid may be potentially useful for selectively increasing methotrexate polyglutamates in tumor cells and (b) introduce another basis for synergism observed between alkaloids and methotrexate. (Author abstract) (25 Refs)

12. RADIOSENSITIZATION OF C3H/HE MAMMARY CARCINOMA BY ADMINISTRATION OF HYPERTHERMIA AND/OR OF MISONIDAZOLE.

Suyama S, Yabumoto E, Furunishi H, Kawanishi K, Yamazaki T, Abe M
Dept. Radiology, Shiga Univ. Medical Sch., Ootsu, Shiga Prefecture, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(10):998-1003 1981

The radiation response of C3H mammary carcinoma subjected to in vivo treatment with hyperthermia and/or misonidazole was studied. C3H mammary carcinoma of the second generation was transplanted sc into the mouse thigh. Tumors were irradiated with 32 Mev electron beams when they reached to a size of 1.3 cm in a mean diameter. Misonidazole of 0.1 mg/g body wt dissolved in normal saline was injected ip 30 min before irradiation. Hyperthermia treatment (43.5 C, 20 min) was made by 2,450 MHz microwave immediately after irradiation. Each tumor was measured daily following irradiation until it reached to the initial tumor size. The dose modification factors were calculated from the growth delay times as well as from the TCD50 values. The DMF calculated from the growth delay times were 1.3, 1.4 and 1.8 for hyperthermia, misonidazole and hyperthermia plus misonidazole respectively in the dose range of more than 2,000 rad. In the dose range of less than 1,000 rad, no significant sensitizing effects of misonidazole and hyperthermia were observed. On the other hand, the combined treatment of hyperthermia with misonidazole produced the same DMF obtained in the dose range of more than 2,000 rad. The DMF calculated from TCD50 values were 1.28, 1.50 and 1.84 for hyperthermia, misonidazole and hyperthermia plus misonidazole respectively. From these results, it can be considered that combined treatment of hyperthermia with misonidazole produces an additive effect. (Author abstract) (20 Refs) (In JPN)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

13. EFFECT OF DOSE FRACTIONATION ON THE ETHYLNITROSOUREA INDUCTION OF SPECIFIC-LOCUS MUTATIONS IN MOUSE SPERMATOGONIA.

Russell WL, Hunsicker PR, Carpenter DA, Cornett CV, Guinn GM
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Proc Natl Acad Sci USA; 79(11):3592-3593 1982

As measured by specific-locus mutations in mouse spermatogonia, fractionating a dose of 100 mg of ethylnitrosourea per kg of body weight into doses of 10 mg/kg injected intraperitoneally at weekly intervals greatly reduces the mutation frequency compared with that from a single dose of 100 mg/kg. Because there is independent evidence that the doses of 10 and 100 mg/kg reach the germ cells in amounts directly proportional to the injected dose, the lower mutational response with the fractionated dose is attributed to repair. The induced mutation rate expected from a single 10-mg/kg dose (on the assumption that this would be 1/10th the rate observed after 10 such doses) would be only 75% of the spontaneous mutation rate. Mouse spermatogonia apparently have an efficient repair system that is effective even against a potent mutagen. (Author abstract) (5 Refs)

14. DOSE-RESPONSE CURVE FOR ETHYLNITROSOUREA-INDUCED SPECIFIC-LOCUS MUTATIONS IN MOUSE SPERMATOGONIA.

Russell WL, Hunsicker PR, Raymer GD, Steele MH, Stelzner KF, Thompson HM
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Proc Natl Acad Sci USA; 79(11):3589-3591 1982

The extreme mutagenic effectiveness of N-ethyl-N-nitrosourea in the mouse has permitted the accumulation of the most extensive dose-response data yet obtained for chemical induction of specific-locus mutations in spermatogonia. In the lower portion of the curve, below a dose of 100 mg/kg, the data fall statistically significantly below a maximum likelihood fit to a straight line. Independent evidence indicates that, over this dose range, ethylnitrosourea reaches the testis in amounts directly proportional to the injected dose. It is concluded that, despite the mutagenic effectiveness of ethylnitrosourea, the spermatogonia are apparently capable of repairing at least a major part of the mutational damage when the repair process is not swamped by a high dose. This finding is important both in basic studies on the mutagenic action of chemicals in mammals and in risk estimation. (Author abstract) (15 Refs)

15. A BIOCHEMICAL STUDY ON COMPENSATORY RENAL ENLARGEMENT IN UNILATERAL NEPHRECTOMIZED RATS TREATED WITH MITOMYCIN C OR 5-FLUOROURACIL.

Takemae K
Dept. Urology, Kanazawa Univ. Sch. Medicine, Kanazawa, Japan
Nippon Hinyokika Gakkai Zasshi; 72(7):865-879 1981

Using Wistar strain male rats (12-16 wk old, av weight 300 g), effects of mitomycin C (MMC) and 5-fluorouracil (5-F) on compensatory renal enlargement after unilateral nephrectomy were examined by measuring the kidney weight, and the amounts of DNA, RNA, and protein. The increase in kidney weight was similar in all groups up to day 10, but at day 14 the weight increase was significantly lower in the animals treated with MMC (0.292 mg/kg) or 5-F (21 mg/kg) than in untreated animals. The ratio of cortical wt to medullary wt remained almost constant throughout the study. The untreated group generally showed a gradual decrease in DNA concentration, while in MMC-treated rats DNA concentration markedly decreased until day 7, suggesting destruction of nuclei; DNA concentration rapidly recovered thereafter. After 5-F treatment, DNA content decreased at a slower rate than that of the MMC group until day 10, then recovered. Total RNA generally increased until day 10 in all groups and then decreased in the MMC and the 5-F groups. A similar pattern was seen with changes in protein. The significance of these findings are discussed with respect to hyperplastic and hypertrophic responses in the untreated and treated groups. (35 Refs) (In JPN)

16. TOXICOLOGY IN MICE OF THE ANTILEUKEMIC AGENT 5-AZA-2'-DEOXYCYTIDINE.

Momparler RL, Frith CH
Departement de Pharmacologie, Universite de Montreal, Montreal, Quebec H3T 1C5, Canada
Drug Chem Toxicol; 4(4):373-381 1981

Preclinical toxicological studies with the new antileukemic agent 5-AZA-2'-deoxycytidine (5-AZA-CdR) on CD2F1 (BALB/c X DBA/2) mice were conducted, including continuous iv infusion, LD50 after 12 hr iv infusion, and acute histopathology and its reversibility after a dose close to the LD50. At a dose of 27.8 mg/kg, the mean survival time of male and female mice was 7.7 and 7.9 days, respectively; the mice lost more than 30% of body weight on day 7 or 8 after the infusion. In the 12 hr iv infusion, 5-AZA-CdR at doses of 14.4 and 27.8 mg/kg produced a leukopenia on days 2-9, with partial recovery on day 10. Surviving mice that had received both treatments remained leukopenic at 43 days after treatment. 5-AZA-CdR produced a pronounced thrombocytopenia on days 5-9 with rebound to above control levels occurring on day 15. 5-AZA-CdR produced bone marrow hyperplasia on day 7 after the iv infusion of 4/6 male mice and 1/7 female mice at doses of 29.2 mg/kg and 18.0 mg/kg, respectively. Normal cellularity was restored in both sexes on day 28. Necrosis of the intestinal mucosa with resultant hyperplasia of the small intestine was observed in 9/10 male and 2/7 female mice after the same treatment. A delayed atrophy of the testes was observed on day 28, but not on day 7, in all male mice. (13 Refs)

17. SYNERGISTIC EFFECT OF PURINE DERIVATIVES ON THE TOXICITY OF PYRAZOFURIN AND 6-AZAURIDINE TOWARDS CULTURED MAMMALIAN CELLS.

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Dept. Biochemistry, McMaster Univ., Hamilton, Ontario L8N 3Z5, Canada
J Cell Physiol; 111(3):291-294 1982

Effects of purine derivatives, adenine, adenosine, hypoxanthine, and guanine on the toxicity of nucleoside analogs pyrazofurin (PF) and 6-azauridine (AU) on cultured Chinese hamster ovary (CHO) cells were determined by examining CHO colony-forming ability in the presence of drugs. The effects of various concentrations of PF on the growth of CH cells was initially determined in suspension culture. In the range of 2-20 nanog (ng)/ml, PF inhibited the growth of CHo cells in a dose-dependent manner; at 2 ng/ml, the effect on cells was minimal, whereas at 20 ng/ml growth rate was markedly reduced. The synergistic effect of various purine derivatives on the toxicity of PF varied with their concentrations; at 2 x 10(-6) M adenine, adenosine, and hypoxanthine caused only a very slight increase in the toxicity of PF. When the purines were present in the growth medium at a final concentration of 5 x 10(-5) M, cell growth was comparatively inhibited by approx 30-, 15-, and 15-fold lower concentrations of PF, respectively. Results suggested that the synergistic effect of PF and purine derivatives was at the level of inhibition of pyrimidine nucleotide synthesis. The purine derivatives exerted a concentration dependent synergistic effect on the toxicity of AU that was very similar to that observed for PF. Results showed that toxicity of both PF and AU towards CHO cells is greatly enhanced by the presence of purines in the medium. (25 Refs)

18. THE TOXICOLOGICAL EVALUATION OF CARMINOMYCIN - AN ANTINEOPLASTIC ANTHRACYCLINE ANTIBIOTIC.

Buroker RA, Johnson DK, Madisson H
Dept. Toxicology, Bristol Lab., Syracuse, NY, 13201
Drug Chem Toxicol; 4(4):383-396 1981

Toxicological evaluation of carminomycin hydrochloride (CH) included single-dose administration of CH iv, sc, and po in rats, mice, dogs, and monkeys, and also multiple-dose iv or sc in rats or dogs. The most prominent clinicopathologic manifestations resulting from the treatment with CH in all single- and multiple-dose studies were dose-related reductions of the total leukocyte, erythrocyte, platelet, and reticulocyte counts, and of the Hb values. The same hematologic parameters were decreased in all species following treatment. The surviving animals, returned to normal or near normal values during the recovery period. Observed histopathologic changes consisted in reduction of numbers of bone marrow cells of both the myeloid and erythroid series and splenic lymphoid and/or reticuloepithelial cells. Enteropathy was observed in the single-dose administration in dogs and in both po and iv in mice. Necrosis, dilatation, and/or epithelial hyperplasia of the Lieberkuhn's crypts occurred, which seemed to be reversible in surviving animals. Increases in blood urea nitrogen, urine protein and urinary casts were seen in all rat studies. Renal changes consisted of dilated tubules containing protein casts, regeneration of the epithelium, and fibrotic, vacuolated, and/or atrophic glomeruli. Reversible, degenerative changes were observed in the seminal vesicles, prostates, and ovaries of rats at higher dose levels, and a decrease in spermatogenesis was observed in some dogs. Cardiac changes were apparent in only 2/20 treated rats, and these inflammatory lesions were considered questionable with regard to cardiotoxic effect of carminomycin. The spectrum of toxic alterations resemble that of other reduced potential for cardiac toxicity in carminomycin hydrochloride-treated animals. (13 Refs)

19. EFFECT OF DIHYDROXYANTHRAQUINONE (NSC 2799836) AND THORACIC IRRADIATION ON LONG-TERM SURVIVAL OF RATS.

Kimler BF, Henderson SD, Mansfield CM, Svoboda DJ, Cheng CC
Radiation Biology Lab., Dept. Radiation Therapy, Univ. Kansas Medical Center, Kansas City, KS, 66103
Cancer Res; 42(7):2656-2659 1982

Dihydroxyanthraquinone (DHAQ: NSC 279836) is a recently synthesized compound that is structurally similar to adriamycin and produces greater antitumor effects in murine model systems. We compared DHAQ to adriamycin in rats, with and without irradiation of the chest at various intervals after drug treatment. A single injection of adriamycin (1 mg/kg ip) had little effect on animal survival, even if combined with radiation (12 Gy 25 MV x-rays), greater than 90% being alive at 1 yr. A single injection of DHAQ (3 mg/kg ip) was equally ineffective up to 200 days after treatment (survival, greater than 90%). However, between 200 and 370 days after treatment, all animals died, producing a median survival time of 280 days. Further, when DHAQ was combined with radiation, there was an increase in animal deaths between Days 30 and 200. For animals irradiated on Days 0, 43, and 93 after DHAQ treatment, only 50, 75, and 80%, respectively, survived to Day 200. All animals that survived past Day 200 subsequently died by 1 yr, displaying the same kinetics of lethality as those animals that had received DHAQ only. A repeat experiment using DHAQ at 1 mg/kg produced similar results. Based on these findings, we conclude that DHAQ produces a long-term (greater than 200 days) toxicity in rats that is not detectable by short-duration toxicity screening. In addition, radiation enhances short-term (less than 200 days) lethality, with the degree of enhancement decreasing as the interval between drug and radiation is increased. (Author abstract) (18 Refs)

20. CHANGES IN MARROW MYELOPOIETIC AND LYMPHOID CELL COUNTS AFTER REPEATED CYCLOPHOSPHAMIDE ADMINISTRATION IN THE RAT.

Berger J
Lab. Haematology, Res. Inst. for Pharmacy and Biochemistry, 533 51 Pardubice-Rosice, Czechoslovakia
Haematologia (Budap); 14(4):407-416 1981

Changes in rat marrow myelopoietic morphology after repeated ip doses of cyclophosphamide (CP) and variations in marrow lymphoid cell counts were studied in adult male (210-240 g body wt) Wistar rats. CP was dissolved in saline and 1 ml/200 g body wt was injected ip within 30 min; a dose of 1.5 mg/kg/day was administered for 28 consecutive days and a dose of 15 mg/kg/day was administered for 21 consecutive days. Relative myelopoietic cell counts (MCC) increased after CP administration in both dose groups. The increase was more marked after the higher dose. Absolute total MCC decreased in both dose groups. The decrease was near to the lower limit of the normal range. Repeated injections of saline did not affect either the relative or the absolute marrow MCC. Significant increase in the relative and decrease in the absolute MCC was observed after restriction of food consumption; the decrease of absolute counts was similar to that observed after application of 15 mg/kg/day CP. Variations of total and individual myeloid cell types were similar. Absolute counts of circulating segmented neutrophils (CSN) slightly increased after 5 mg/kg/day CP dose and returned to normal in 4 wk after drug withdrawal. Absolute counts of CSN increased markedly after CP withdrawal in the 15 mg/kg/day group. The changes of absolute counts of circulating and marrow segmented neutrophils were not correlated in any dose group. Absolute and relative marrow lymphoid cell counts decreased markedly in the 5 mg/kg/day group and these cells were missing in the femoral marrow in the 15 mg/kg/day group. Full recovery of marrow lymphoid cell counts took 7 days after discontinuation of CP in the 5 mg/kg/day group while in the 15 mg/kg/day group the counts improved but full recovery could not be observed as all animals died. Results confirmed previous data on circulating hypersegmented neutrophils. (21 Refs)

21. PROTECTION AGAINST MISONIDAZOLE-INDUCED TOXICITY IN VITRO BY NON-STEROIDAL ANTI-INFLAMMATORY AGENTS.

Millar BC, Jinks S
Radiobiology Unit, Physics Dept., Inst. Cancer Res., Clifton Ave., Sutton, Surrey, England
Int J Radiat Oncol Biol Phys; 8(3/4):795-797 1982

Protection against toxic effects of misonidazole (MISO) was studied in asynchronous cultures of Chinese hamster cells V-79-753B. Overnight exposure of the cells to benoxaprofen (5 x 10(-5) M), indomethacin (5 x 10(-5) M), or aspirin (10(-4) M) protected cells against MISO-induced toxicity in air and hypoxia at 37 C. In each instance the amount of protection afforded by the agents was equivalent to a dose-reduction factor of approx 1.5-2.0 for cells in hypoxia. The principal effect of MISO in benoxaprofen-treated cells was observed as an increase in the shoulder region of the toxicity curve. (16 Refs)

22. A BIOCHEMICAL NEUROTOXICITY STUDY RELATING THE NEUROTOXIC POTENTIAL OF METRONIDAZOLE AND NITROFURANTOIN WITH MISONIDAZOLE.

Rose GP, Dewar AJ, Stratford IJ
Shell Res. Ltd., Sittingbourne Res. Center, Sittingbourne, Kent ME9 8AG, England
Int J Radiat Oncol Biol Phys; 8(3/4):781-785 1982

The neurotoxic potential of metronidazole and nitrofurantoin was studied in Wistar rats measuring the activity of beta-glucuronidase (BGU) and beta-galactosidase (BGA) in homogenates of nervous tissue. The effect of metronidazole administration on the BGU and BGA activity in the sciatic/posterior tibial nerve (SPTN) and trigeminal ganglia is presented. Significant increases in both enzymes were observed in the distal section of the SPTN in both the 400 and 800 mg/kg daily dose groups. Results suggested that metronidazole has a threshold to its neurotoxic effect and that further administration of the drug does not increase the degree of nerve-damage produced. (21 Refs)

PHARMACOKINETICS OF ANTITUMOR AGENTS

23. DISPOSITION AND METABOLIC PROFILE OF A NEW ANTITUMOR AGENT: CL 216,942 (BISANTRENE) IN LABORATORY ANIMALS.

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(c/o Nicolau) Dept. Pharmacodynamics, Medical Res. Div., American Cyanamid Co., Pearl River, NY, 10965
Cancer Treat Rep; 66(5):1173-1185 1982

A 14C-labeled antitumor drug, CL 216,942 (bisantrene), was administered iv at doses of 1-20 mg/kg to the monkey, dog, and rat. The serum concentration versus time profiles indicated at least a biphasic disappearance of the drug with long elimination half-lives of about 2-8 days in all three species. Total recoveries in the excreta collected through Day 7 were low (less than 50% of the administered dose), especially in the monkey and dog, with most of the drug found in the feces. Volumes of distribution in the central compartment as well as tissue distribution studies in all three species indicated no evidence of significant concentration of the drug with long elimination half-lives in a deep compartment. The same organs and tissues (heart, liver, kidney, pancreas, spleen, lymph nodes, bone marrow and most of the highly perfused glands) contained the highest drug concentrations in all three species. Metabolism studies indicated no evidence of significant biologic transformation of the drug in these species. In vitro studies by equilibrium dialysis indicated significant binding of the drug to DNA by intercalation. (Author abstract) (3 Refs)

24. MACROMOLECULAR INTERACTIONS OF [14C-RING]MELPHALAN IN BLOOD.

Ahmed AE, Hsu TF, El-Azhary RA, Moawad H, Costanzi J
Dept. Pathology, Pharmacology and Toxicology, Medicine, Univ. Texas Medical Branch, Galveston, TX, 77550
Biochem Pharmacol; 31(8):1615-1619 1982

The pharmacokinetics and macromolecular interactions of [14C-ring]melphalan (L-PAM) in blood were studied in rats following a single oral dose (20 mg/kg, 0.1 mCi/kg). Radioactivity levels were monitored in blood over a period of 72 hr. The highest levels of radioactivity were observed at 2 hr. The decline of radioactivity from the blood was biphasic with T1/2alpha = 7 hr and T1/2beta = 75 hr. The radioactive species in plasma corresponded to unchanged L-PAM and its two known hydrolytic products 4,2-hydroxyethyl 2-chloroethylamino-L-phenylalanine (L-MOH) and 4[bis(2-hydroxyethyl)amino]-L-phenylalanine (L-DOH). In addition, four other major, previously unknown, metabolites of L-PAM were detected in plasma. At 72 hr, most of the radioactivity was bound to macromolecular components, 26% to plasma macromolecules and 62% in red blood cells. Covalent binding to blood cells was mainly to membrane proteins. Binding to hemoglobin and other soluble components of the red cells was also observed, with a 5,000-fold greater affinity for membranes. These studies suggest extensive interaction of melphalan, or its metabolites, with membrane and soluble proteins of red blood cells. (Author abstract) (24 Refs)

25. BODY RESIDUE AND METABOLISM OF ADRIAMYCIN AND DAUNORUBICIN IN CONTROL AND PHENOBARBITAL-PRETREATED MICE.

Bolanowska W, Gessner T
Dept. Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Inst., Buffalo, NY, 14263
Xenobiotica; 12(2):125-136 1982

Metabolism of adriamycin (ADR) and daunorubicin (DR) was investigated in DBA/2Ha mice after ip injection and compared with that in phenobarbital-pretreated animals. At 24 hr after drug administration 83% of ADR and 67% of DR derived fluorescence were recovered from cadavers and excreta. Destruction of anthracyclines in excreta to non-fluorescent materials could be partly responsible for the low recoveries. ADR was metabolized to a limited extent in mice. At 24 hr 70% dose was detected as the unchanged drug and only 13% as its deoxyaglycones. DR was metabolized more extensively. At 24 hr 29% of the dose was as the unchanged drug, while 32% was present as daunorubicinol (DROL) and 16% as aglycones. Phenobarbital did not significantly affect these parameters. In phenobarbital-pretreated mice there was a marked increase in the amounts of ADR or DR aglycones in the liver, and a decrease in the levels of unchanged ADR or DR. (Author abstract) (38 Refs)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

26. STUDIES OF A NEW ANTITUMOR HYDRAZINE (AT-1902).

Ren Y, Shu H, Zhang T, Chen Z, Lin C
Inst. Materia Medica, Academia Scinica, Shanghai, People's Republic of China
Kexue Tongbao; 26(17):1078-1080 1981

Synthesis and pharmacological activities are described for the new hydrazine antitumor agent (AT-1902). The LD50 in mice were 1,736 mg/kg ip and 1,343 mg/kg po. Its subacute toxic dose (iv or po) in rabbits and dogs was 10-15 mg/kg/day x 7 days. AT-1902 exhibited significant inhibitory activities on rat W-256 carcinoma, murine Ehrlich carcinoma and hepatoma, with tumor inhibition of 55% to 84% at doses of 200-250 mg/kg for 5 to 10 days. It also showed activities on other experimental tumors. Its chemical structure is given. (4 Refs) (In CHI)

27. CYTOTOXIC EFFECT OF THE CULTURE SUPERNATANT OF CLOSTRIDIUM TETANI.

Matsunaga T, Miyamoto K, Koshiura R
Dept. Pharmacology, Hokiruki Univ. Sch. Pharmacy, Ho-3, Kanagawa-machi, Kanazawa, 920-11, Japan
Chem Pharm Bull (Tokyo); 30(2):702-707 1982

Cytotoxic effect of the culture supernatant (CS) of Clostridium tetani on mouse leukemia L1210 cells is discussed. The cytotoxic activity of the CS increased with the growth of the organism and reached a steady level between 24-72 hr; subsequently it tended to decrease gradually. CS obtained by cultivation for 24 hr was fractionated by addition of ammonium sulfate, the precipitate formed was dissolved in phosphate-buffered saline (PBS), and dialyzed. The cytotoxic activity was eluted as two peaks in parallel with the hemolytic activity suggesting that one of the cytotoxic substances might be tetanolysin and the other a high molecular hemolysin. When the low molecular fraction was preincubated with cholesterol, the cytotoxic activity decreased and was completely inhibited by 10(-6) M cholesterol. Comparative cytotoxicity to L1210 cells of the two fractions and theta-toxin is presented. Two hemolysins derived from C tetani were cytotoxic to similar extent and approx 1.3 hemolytic units/ml were required to induce 50% inhibition of the cell growth. On combined treatment with 5-fluorouracil (5-FU) and tetanolysin, the cell growth was inhibited by approx 27.1%. When various amounts of tetanolysin were combined with 5-FU, smaller amounts of tetanolysin showed more potent combination effects than larger amounts. (18 Refs)

28. MOLECULAR PHARMACOLOGY OF THE ANTHRACYCLINE DRUG 9,10-ANTHRACENEDICARBOXALDEHYDE BIS[(4,5-DIHYDRO-1H-IMIDAZOL-2-YL)HYDRAZONE] DIHYDROCHLORIDE (CL 216,942).

Bowden GT, Garcia D, Peng YM, Alberts DS
Dept. Radiology, Div. Radiation Oncology, Coll. Medicine, Univ. Arizona, Tucson, AZ, 85724
Cancer Res; 42(7):2660-2665 1982

A new anthracene bishydrazone derivative, 9,10-Anthracenedicarboxyaldehyde bis[(5-dihydro-1H-imidazol-2yl)hydrazone] dihydrochloride (Cl 216,942) has shown antitumor activity in Phase I trials against both hematological cancers and solid tumors. The effects of Cl 216,942 on L1210 mouse leukemia cells were studied with the nucleoid sedimentation and alkaline elution assays. Evidence for Cl 216,942 intercalation into cellular DNA was obtained in exponentially growing cells by comparing the L1210 nucleoid sedimentation behavior in neutral sucrose gradients of ethidium bromide with nucleoids from Cl 216,942-treated cells. A 1-hr treatment of exponentially growing L1210 cells with Cl 216,942 induced both protein-associated DNA single-strand breaks and DNA-protein cross-links as detected by the alkaline elution assay. The DNA strand break and DNA-protein cross-link frequencies were found to be within a factor of 2 of each other over a range of Cl 216,942 concentrations. The dose response for the induction of DNA damage showed a linear increase up to 10 ug/ml, but this was followed by a decrease in damage at dose levels greater than 10 ug/ml. The biphasic dose response could not be explained by changes in the cellular uptake of Cl 216,942. The kinetics of Cl 216,942 induction of DNA damage after a 1-hr treatment showed that at the dose which gave maximum damage the degree of damage (10 ug/ml) decreased with further incubation, but at a higher dose (20 ug/ml) DNA damage increased with postincubation at 37 C. The cytotoxicity produced by Cl 216,942 at a given frequency of protein-associated strand breaks was low. Cl 216,942 thus appeared to belong to a low-toxicity group of DNA intercalators. (Author abstract) (17 Refs)

29. ANTITUMOR AND TOXIC PROPERTIES OF RETINOID C15.

Afanas'ev IuI, Nozdrin VI, Bakhshinian MZ, Samokhvalov GI, Vakulova LA, Iakovleva IM
Dept. Histology and Embryology, I. M. Sechenov First Medical Inst., Moscow, USSR
Biull Eksp Biol Med; 93(4):76-78 1982

Antitumor activity and toxicity of synthetic metabolite of vitamin A (retinoid C15) were studied in C57BL/6 mice with transplanted Lewis lung carcinoma and cervical carcinoma, and in CBA mice with transplanted stomach carcinoma. The animals received ip injections of retinoid C15 (0.2-1.6 mg, qod). Retinoid C15 was less toxic than retinoic acid (max permissible doses were 1.5 g/kg and 0.3 g/kg, respectively). Retinoid C15 inhibited the growth of transplanted tumors. Retinoid C15 did not inhibited the hematopoiesis and phagocytic activity of macrophages in tumor-bearing animals. (7 Refs) (In RUS)

30. EXAMINATION OF NEWLY SYNTHESIZED 2-CHLOROETHYLNITROSOUREAS IN PRETERMINAL LEUKEMIA L 5222 AND IN TWO TRANSPLANTED NEUROGENIC TUMORS.

Berger M, Zeller WJ, Eisenbrand G, Lin PZ, Nakra M, Schmahl D
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Arzneim Forsch; 32(5):481-484 1982

The chemotherapeutic activities of 11 chloroethylnitrosoureas, among them 10 newly synthesized compounds, were investigated in rat leukemia L 5222 and in two neurogenic rat tumors. 1-(4-Amino-2-methyl-5-pyrimidinyl)-methyl-3-(2 chloroethyl)-3-nitrosourea hydrochloride and cyclophosphamide served as reference substances. The newly synthesized compounds were 1-(2-chloroethyl)-1-nitro-3-(2-carboxyethyl)-urea, 1-(2-chloroethyl)-1-nitroso-4-methyl-4-formyl semicarbazide, 1-(2-chloroethyl)-1-nitroso-3-(methylene-2-pyridyl) urea, 1-(2-chloroethyl)-1-nitroso-3-(methylene-2-pyridyl) urea hydrochloride, 1-(2-chloroethyl)-1-nitroso-3-(methylene-4-pyridyl) urea hydrochloride, 1-(2-chloroethyl)-1-nitroso-3-(3-pyridino)-urea (7), 1-(2-chloroethyl)-1-nitroso-3-(3-pyridyl)-urea hydrochloride (8), 1-(2-chloroethyl)-1-nitroso-3-[4(2,6-dimethyl morpholino)]-urea, 1-(2-chloroethyl)-1-nitroso-carbamoyl-morpholine, 1-(2-chloroethyl)-1-nitro-carbamoyl-2,6-dimethyl morpholine (11). Against both neurogenic tumors cyclophosphamide was distinctly superior to all nitrosoureas. In leukemia L 5222 all nitrosoureas except compounds 7, 8, 11 effected cures. Remarkable differences in toxicity could be observed between the nitroso compounds investigated. (8 Refs)

31. NEW NITROSOUREA DERIVATIVES AND RELATED COMPOUNDS.

Imbach JL, Martinez J, Oiry J, Bourut C, Chenu E, Maral R, Mathe G
Laboratoire de Chimie Bio-Organique, ERA-CNRS no. 195, Universite des Sciences et Techniques du Languedoc, Place Eugene Bataillon, 34060 Montpellier, Cedex, France
INSERM Symp; 19:123-137 1981

Chemical studies and biological activity tests of new nitrosourea derivatives against L1210 leukemia and other murine tumors are described. The acute toxicities in mice of N,N'-bis(N-(2-chloroethyl)N-nitroso carbamyl)cystamine (CNCC) and 3-(2-chloroethyl)3-nitroso-1-[2,3-isopropylidene-5 (nitro-4-benzoyl)-1-ribofuranosyl]urea (RFCNU) are very close, and less than those of other nitrosoureas. The oral toxicity of CNCC is lower than that of RFCNU. (17 Refs)

32. NOVEL LIPOPHILIC NITROSOUREAS.

Bigler AJ, Buus L, Bregnedal P, Svendseen O, Atassi G, Muntzing J, Jensen G
Medical Dept., H. Lundbeck and Co., Ottiliavej 7-9, DK 2500 Valby, Denmark
INSERM Symp; 19:113-122 1981

Synthesis and preliminary testing are reported for a series of nitrosourea derivatives possessing much greater lipophilicity than well-known nitrosoureas. Testing included ip administration of drug in the P-388, L1210, B16 melanoma, colon adenocarcinoma 26, Lewis lung carcinoma, and ependymoblastoma models, and po administration against L1210 and Harding-Passey melanoma models. Activities of the derivatives varied among the models; toxicity was generally higher than for standard nitrosoureas, but was of relatively short duration. (no Refs)

33. CHEMOTHERAPEUTIC ACTIVITY OF 2-CHLOROETHYLNITROSOCARBAMOYL DERIVATIVES OF AMINO ACIDS IN A TRANSPLANTED RAT LEUKEMIA (L 5222).

Zeller WJ, Berger M, Eisenbrand G, Tang W, Schmahl D
(c/o Schmahl; Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Arzneim Forsch; 32(5):484-486 1982

The therapeutic activity of a single-dose treatment with 14 2-chloroethylnitrosocarbamoyl derivatives of amino acids (CNU-analogs) in L 5222 rat leukemia is presented. Compounds under study included free carboxylic acids, a methylester, a toluidide, four glucosamides and one derivative of a dipeptide. All substances proved to be active effecting at least an increase in life span of greater than or equal to 120% compared with untreated controls at the optimal dose; two compounds effected isolated cures (90-day survivors). Compared with previous data obtained with established and new nitrosoureas under the same conditions, the effectivity of the compounds presented here should be classified, however, only as moderate. (Author abstract) (9 Refs)

34. ANTITUMOR EVALUATION OF SOME NEW PLATINUM COMPOUNDS.

Rochon FD, Kong PC
Chemistry Dept., Universite du Quebec a Montreal, C.P. 8888, Montreal, H3C 3P8, Canada
J Clin Hematol Oncol; 12(2):39-43 1982

The antitumor activities of six new platinum compounds against P388 and L1210 leukemias were evaluated. NSC 267895 showed max ratio of test evaluation to control (T/C) expressed as a percentage (140%) at a concentration of 6.25 mg/kg and was classified 1D (deferred). NSC 276441 and NSC 291071 were also classified 1D. Of the three compounds with the benzenetetracarboxylate ligand, the amine compound (NSC 324329) was toxic at a concentration greater than 3 mg/kg (best T/C of 150% at 1.56 mg/kg) and was selected for further testing. The cyclopentylamine (NSC 324330) and methylamine (NSC 324331) complexes were slightly less active. (4 Refs)

STUDIES OF ANTIMETASTATIC AGENTS

35. EXPERIMENTAL STUDY FOR LUNG METASTASES OF UNDIFFERENTIATED SARCOMA TRANSPLANTED TO THE EXTREMITY OF MICE.

Tatezaki S, Matsui T, Tsuji A
Dept. Orthopedics, Toyama Medical and Pharmacological Univ., Toyama, Japan
Nippon Seikeigeka Gakkai Zasshi; 55(9):1100-1101 1981

No decrease in the vol of transplanted spontaneous C3H mouse tumor was observed in mice treated with 100 mg/kg of cyclophosphamide. A significant suppression (t = 5.89, p less than 0.01) was found when compared to controls. Lung metastasis and death rate were also significantly less (chi2 = 21.7, p less than 0.005, and chi2 = 33.2, p less than 0.005, respectively). For the radiation therapy group, tumor vol and death rate were significantly decreased (t = 11.5, p less than 0.01, chi2 = 7.59, less than 0.01 respectively), but lung metastasis was seen in the surviving mice. Compared to radiation therapy, chemotherapy markedly increased survival rate and the suppression of lung metastasis. (no Refs) (In JPN)

36. ANTITUMOUR AND ANTIMETASTATIC ACTION OF BIS-2,2'-DICHLORDIETHYL AMMONIUM SALT OF DINITRILE OF 2,4-DINITRO-3-PHENYLGLUTARIC ACID.

Astardjieva ZL, Stoychkov JN
Oncological Res. Inst., Medical Acad., 1156 Sofia, Bulgaria
Dokl Bolg Akad Nauk; 34(12):1757-1759 1981

The effects of bis-2,2'-dichlordiethyl ammonium salt of 2,4-dinitro-3-phenylglutaric acid (NIO 7901) on growth and metastasis of Lewis lung carcinoma (LLC) in C57Bl and BDF1 mice of both sexes were studied. LLC cells were injected im and treatments were employed at varying doses and on a continuous and an interrupted schedule in both breeds of mice. Early application of NIO 7901 in two courses (2 x 4 days) in total doses of 400 and 800 mg/kg lead to tumor growth inhibition of greater than 50% in C57Bl mice. Lower doses (100 and 200 mg/kg) lead to almost as much inhibition. Early treatment (days 1-11) with total doses from 137.5 to 825 mg/kg resulted in a dose-dependent inhibition of tumor growth, with 50% inhibition observed with both 550 and 825 mg/kg doses. The effect of 400 mg/kg treatment in the interrupted (2 x 4 day) schedule was similar to the 500 mg/kg dose in the 1-11 day schedule. With BDF1 mice the 10-day continuous course at total doses of 660 and 880 mg/kg yielded tumor growth inhibition of 61.4% and 67.9%, respectively, but the two-course injection (2 x 5 days) had no antitumor effect. The number of metastases in the lungs of BDF1 mice decreased in response to late treatment even when the tumor growth was not affected. (3 Refs)

37. INTERFERON INCREASES HLA SYNTHESIS IN MELANOMA CELLS: INTERFERON-RESISTANT AND -SENSITIVE CELL LINES.

Basham TY, Bourgeade MF, Creasey AA, Merigan TC
Div. Infectious Diseases, Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Proc Natl Acad Sci USA; 79(10,part1):3265-3269 1982

We report that human leukocyte interferon preparations increase the expression of beta2-microglobulin by 100-200% on the surface of normal fibroblast and melanoma cell lines sensitive to interferon. This increase in expression can be correlated with an increase in HLA synthesis as measured by incorporation of [35S]methionine in these antigens. This enhanced HLA synthesis, which is 5-to 17-fold, is time dependent and dose related. Synchronized cells in the G0/G1 phase of the cell cycle appear to be more sensitive to this interferon action. Neither an increase in surface expression nor in HLA synthesis is observed in a melanoma cell line resistant to the antiviral and antigrowth effects of interferon. Furthermore, there appears to be a stronger correlation between this increased HLA synthesis and the antiviral function that between it and the antiproliferative action of interferon. (Author abstract) (18 Refs)

38. IN SITU ACTIVATION OF TUMORICIDAL PROPERTIES IN RAT ALVEOLAR MACROPHAGES AND REJECTION OF EXPERIMENTAL LUNG METASTASES BY INTRAVENOUS INJECTIONS OF NOCARDIA RUBRA CELL WALL SKELETON.

Sone S, Fidler IJ
(c/o Fidler) Cancer Metastasis and Treatment Lab., NCI-Fredrick Res. Facility, P.O. Box B, Fredrick, MD. 21701
Cancer Immunol Immunother; 12(3):203-209 1982

Influence of systematically administered squalene-treated cell wall skeleton of Nocardia rubra (N-CWS) on the tumoricidal properties of rat alveolar macrophages (AM) and on levels of AM activation sufficient to eradicate established experimental pulmonary metastases of a syngeneic mammary adenocarcinoma was studied in specific pathogen-free inbred F344 (5-7 wk old) female rats. Significant and reproducible cytotoxicity was mediated by AM harvested from rats that had received N-CWS iv. Injection of N-CWS placebo did not render AM tumoricidal. Statistically significant levels of cytotoxicity were mediated by AM harvested from rats injected with more than 150 ug N-CWS. Reproducible maximal levels of tumor cytotoxicity were obtained with 300 ug N-CWS iv/rat; AM remained tumoricidal for 48-72 hr. In experiments where N-CWS was injected sc, ip, or iv, only AM from iv-injected rats were tumoricidal. Data agreed with previous results showing that the activation of macrophages at a given anatomical site requires that the activating stimulus be delivered to the macrophages. All the rats treated with Hanks' balanced salt solution or N-CWS placebo preparations had developed lung tumor colonies (LTC). In contrast, 11/13 treated rats with N-CWS were free of visible LTC. Data suggested that established parenchymal pulmonary micrometastases could be eradicated by iv injections of N-CWS. (29 Refs)

INTERFERON AND OTHER ANTIVIRALS

39. SENSITIVITY OF CULTURED HUMAN OVARIAN CARCINOMA CELLS TO INTERFERONS OF DIFFERENT ORIGIN.

Timofeev IV, Krispin TI, Shloma DV
N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Vopr Virusol; (2):228-230 1982

Antiproliferative effect of human, porcine, and bovine interferons (IF) was studied in cultured cells of human ovarian carcinoma (OC). Both homologous and heterologous (porcine) IF produced concentration-dependent inhibition of DNA biosynthesis in OC cells (18.2-50.5% and 18.2-68.4%, respectively). Bovine IF caused less marked inhibition of proliferative activity (6.6-43.6%). (8 Refs) (In RUS)

40. INHIBITION OF MOUSE FIBROBLAST INTERFERON BY GANGLIOSIDES. DIFFERENTIAL EFFECTS ON BIOLOGICAL ACTIVITY AND ON INDUCTION OF (2'-5')OLIGOADENYLATE SYNTHETASE.

Krishnamurti C, Besancon F, Justesen J, Poulsen K, Ankel H
Dept. Biochemistry, Medical Coll. Wisconsin, Milwaukee, WI, 53226
Eur J Biochem; 124(1):1-6 1982

Gangliosides are potent inhibitors of the antiviral activity of mouse fibroblast and other beta-interferons. We have compared the effects of gangliosides on antiviral and antigrowth activities of mouse fibroblast interferon and on the induction of (2'-5')oligoadenylate synthetase, one of the enzymes implicated in the antiviral state induced by interferon. Whereas both biological effects appear to be inhibited by gangliosides in an analogous fashion, inhibition of induction of (2'-5')oligoadenylate synthetase does not correlate with inhibition of vesicular stomatitis virus replication. Ganglioside concentrations that inhibit the interferon-induced (2'-5')oligoadenylate synthetase to levels close to those of uninduced cells, still allow for a 100-1,000-fold reduction of viral yield. Significantly higher ganglioside concentrations are required to prevent completely the antiviral effect. This biphasic relationship between (2'-5')oligoadenylate synthetase levels and inhibition of viral yield suggests that no or very small increases in synthetase levels are involved in inhibition of virus by between two and three orders of magnitude. (Author abstract) (35 Refs)

OTHER RELATED STUDIES

41. A MODEL TO STUDY DRUG EFFECTS ON LYMPHOMA AND NORMAL CELL POPULATIONS USING THE AKR/J MOUSE.

Schwartz GN, Biegel JA, Boggs SS
Dept. Experimental Hematology, Defense Nuclear Agency, Armed Forces Radiobiology Res. Inst., Bethesda 8, MD, 20814
Leuk Res; 6(2):269-279 1982

Origin and growth pattern of a long passaged AKR(Rb6.15)1A1d lymphoma are described. Characteristics of this model system were used to compare the effects of 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) and spirogermanium (SG) on transplanted lymphoma and host normal cell populations within a single animal. AKR mice with terminal stages of the long-passaged lymphomas showed evidence of such neurological complications as rolling, ataxia, or paralysis. The spleen and inguinal lymph node were enlarged compared to these tissues in normal AKR mice. Twenty-five days after the injection of 10(6) bone marrow, spleen, or thymus cells from non-leukemic AKR(Rb6.15)1A1d mice, a small number of donor-type metaphase cells (4.5 +-2.60%) was found in the spleens of five AKR/J recipient mice. At day 4, 24 hr after drug treatment of lymphoma-bearing AKR mice, the percentage of donor-type metaphase cells decreased from approx 51% in non-treated mice to 39% in mice given 70 mg/kg SG, and to 19% in animals injected with 4.4 mg/kg BCNU. Even tough no significant increase in the percentage of donor-type metaphase cells was observed in the marrow of SG treated mice, this appeared to be the result of an increase in the number of host-type metaphase cells, rather than a decrease in the number of donor-type metaphase cells. However, in the BCNU treated mice a significant decrease in the number of donor-type metaphase cells was observed, with no change in the number of host-type metaphase cells/humerus. SG had little effect on total marrow cellularity, but a significant reduction existed in the total number of cells and in the number of peroxidase-positive cells in the marrow of BCNU treated animals. (33 Refs)

42. ENHANCING EFFECT OF ADRIAMYCIN ON THE METASTASIS OF EXPERIMENTAL TUMOR: PART I.

Watanabe H, Chigira M, Maebara S, Nagase M, Yabata N, Udagawa H, Takenichi Y
Dept. Orthopedics, Gunma Univ., Maebashi, Gunma, Japan
Nippon Seikeigeka Gakkai Zasshi; 55(9):1103-1104 1961

Lung metastasis was noticed when Lewis lung carcinoma was grafted to C57BL/6 mice treated ia with adriamycin (ADR) at 2 mg/kg, but not in those treated with iv injection or only locally. The ia treatment of ADR 15 days after transplantation even increased lung metastasis to 109.4% compared to control. Chemotherapeutic agents, such as ADR, that markedly damage blood vessels must be reexamined. (no Refs) (In JPN)

43. CYTOTOXICITY AND DNA STRAND BREAKS BY 5-IMINODAUNORUBICIN IN MOUSE LEUKEMIA L1210 CELLS: COMPARISON WITH ADRIAMYCIN AND 4'-(9-ACRIDINYLAMINO)METHANESULFON-M-ANISIDIDE.

Zwelling LA, Kerrigan D, Michaels S
NCI, Building 37, Room 5D17, 9000 Rockville Pike, Bethesda, MD, 20205
Cancer Res; 42(7):2687-2691 1982

The effects upon cellular DNA and cytotoxicity produced by the anthracyclines 5-iminodaunorubicin and adriamycin were studied in mouse leukemia L1210 cells. 5-Iminodaunorubicin produced protein-concealed DNA strand breaks as measured by alkaline elution as had other intercalators including adriamycin. 5-Iminodaunorubicin produced DNA breaks more more efficiently than did adriamycin despite a lower potency for free radical formation. Many of the 5-iminodaunorubicin breaks measured in this assay may arise from apposed single-strand breaks (ie, double-strand breaks). 5-Iminodaunorubicin produced breaks which disappeared within 1 and 2 hr following drug removal and were in this way similar to the breaks produced by the acridine intercalator 4'-(9-acridinylamino)methanesulfon-m-anisidide. Adriamycin produced more persistent breaks. Despite similarities in the kinetics of break disappearance, 5-iminodaunorubicin produced greater cytotoxicity than did 4'-(9-acridinylamino)methanesulfon-m-anisidide when compared at doses producing equal single-strand or double-strand breaks. Differences in the ratio of single-strand breaks to double-strand breaks and the associated cytotoxicity for 4-iminodaunorubicin and 4'-(9-acridinylamino)methanesulfon-m-anisidide indicate that a different mechanism is probably involved in the DNA break production by each agent. Differences between the cytotoxicity associated with the DNA break production by two agents with similar break disappearance kinetics indicate that intercalator-induced DNA breaks cannot be a uniformly lethal DNA lesion. (Author abstract) (22 Refs)

44. EFFECTS OF TWO SELECTED PIPERAZINE DERIVATIVES ON EXCRETION OF 125I-IODODEOXYURIDINE IN MICE WITH TRANSPLANTED L-1210 LEUKEMIA.

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Zaklad Farmakodynamiki, Akademia Medyczna, ul. Narutowicza 120 a, 90-145 Lodz, Poland
Acta Pol Pharm; 38(6):717-721 1981

The effects of two piperazine derivatives (pipobromane: 1/10 and 1/2 LD50 ip compound NG: 1/10 and 1/2 LD50 and LD10 ip) on the excretion of 125I-iododeoxyuridine were studied in DBA/2 and hybrid Swiss x DBA/2 mice with transplanted L-1210 leukemia, and were compared with that of cyclophosphamide (1/10 and 1/2 LD50 ip). All compounds were administered 24 hr after leukemia cell transplantation. The rates of 125I excretion were determined in vivo by measuring the total body radioactivity. Pipobromane was found to be less cytotoxic for L-1210 cells than cyclophosphamide. Compound NG did not accelerate the 125I excretion even when given at the max tolerable dose (LD10-490 mg/kg). The antileukemic action of compound NG in mice with transplanted L-1210 leukemia may be the result of the cytostatic effect of this substance. (14 Refs) (In POL)

45. INFLUENCE OF A PORTACAVAL SHUNT ON THE DISTRIBUTION OF 14C-CHOL-PC-DCP-LIPOSOMES AND LIPOSOME ENTRAPPED 3H-METHOTREXATE IN THE ORGANS OF RATS.

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Hepatogastroenterology; 28(2):90-92 1981

The individual roles of hepatic parenchymal cells and non-parenchymal cells in the uptake of iv injected liposomes by the liver have not yet been clearly determined. Experimentally, it is suggested that a portacaval shunt reduces the phagocytic capacity of the liver RES. In our experiments a portacaval shunt does not influence the hepatic uptake of 14C-Chol-PC-DCP-liposomes and the liposome entrapped 3H-Methotrexate in rats. In normal rats and in rats with a portacaval shunt, most of the 14C- and 3H-radioactivity is found in the liver and the ratio between the amounts of free and liposome entrapped radioactivity 3 to 15 hr after iv injection is approx 1:10. Therefore, it is concluded that the liver RES does not play an integral role in the enrichment of liposomes in the liver. (Author abstract) (20 Refs)

46. TISSUE CONCENTRATION OF METHOTREXATE IN OSTEOSARCOMA.

Amino K, Furuya K, Arai T, Kawaguchi T, Wada N, Matsumoto S

Dept. Orthopedics, Tokyo Medical and Dental Univ., Tokyo, Japan

Nippon Seikeigeka Gakkai Zasshi; 55(10):1503-1505 1981

Various amounts of a combination of methotrexate-H3 (MTX-H3) and Citrovorum factor (CF) were given sc to three groups of nude mice (4 in each group) carrying human osteosarcoma. The amount of MTX-H3 taken into the tumor decreased as a function of time, but the concentration of MTX equivalent (MTX and metabolic products of MTX, such as MTX polyglutamate and 7-OH-MTX) was proportional to the amount of MTX given. CF reduced the MTX concentration in the tumor. In each group, MTX-equivalent was stored more in liver and kidney than in serum, muscle, or brain. The values obtained with enzyme assay were lower than those with radioassay, suggesting storage of MTX metabolic products. Active MTX that inhibits dihydrofolate reductase was found in the tumor (1 x 10(-7) M). The percent of active MTX for the group given 14.4 mg/kg was 85%, and was 12% for the group given 100 mg/kg, suggesting that the effective amount in the tumor will not increase with the increase of the dose. Autoradiography, specimen prepared by cryostat sectioning showed many grains, but few were seen in Spurr resin treated specimen. From the latter MTX-H3 might have been washed out. (no Refs) (In JPN)

47. ROLE OF DEPHOSPHORYLATION IN ACCUMULATION OF 1-BETA-D-ARABINOFURANOSYLCYTOSINE 5'-TRIPHOSPHATE IN HUMAN LYMPHOBLASTIC CELL LINES WITH REFERENCE TO THEIR DRUG SENSITIVITY.

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Cancer Res; 42(7):2846-2851 1982

After a 3-day exposure to 0.1 uM 1-beta-D-arabinofuranosylcytosine (ara-C) in culture, growth was inhibited to 5.6% in MOLT-4F, 25% in Raji, and 91% in Daudi cells compared with control. Growth inhibition was more profound when exposure time was extended up to 7 days. Inhibition of DNA synthesis varied with sensitivity to ara-C. Plateau levels of intracellular 1-beta-D-arabinofuranosylcytosine 5'-triphosphate (ara-CTP) were 35.5, 13.4, and 3.6 nmol/10(9) cells exposed to 0.1 uM ara-C in MOLT-4F, Raji, and Daudi cells, respectively, corresponding to the sensitivity to ara-C. The nucleotide levels at the plateau, however, did not correspond to the initial levels of the ara-CTP or to the calculated rate of ara-CTP synthesis, which decreased from Raji to MOLT-4F to Daudi cells. Ara-C deamination had negligible effect on the differential accumulation of ara-CTP. Ara-CTP degradation due to dephosphorylation was marked in Raji and Daudi cells but slight in MOLT-4F cells. The half-life of intracellular ara-CTP was 204, 26.4, and 31.1 min in MOLT-4F, Raji, and Daudi cells, respectively. The ara-CTP level was considered to be maintained bimodally by synthesis and degradation of the nucleotide. This conclusion was supported by the fact that, in Raji and Daudi cells exposed to 0.1 uM ara-C in the presence of 1 mM hydroxyurea, the plateau levels of ara-CTP increased 3-fold through inhibition of the nucleotide degradation. Thus, not only ara-C phosphorylation but also subsequent ara-CTP dephosphorylation was important in the accumulation and maintenance of ara-CTP and in the sensitivity to ara-C. (Author abstract) (46 Refs)

48. EFFECT OF THE TIME OF CYCLOPHOSPHAMIDE ADMINISTRATION ON THE RHYTHM OF ALPHA-FETOPROTEIN LEVEL IN THE SERUM OF MICE WITH HEPATOMA 22A AND PROLIFERATION OF TUMOR CELLS.

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Biull Eksp Biol Med; 93(4):73-75 1982

Diurnal rhythms of serum level of alpha-fetoprotein (AFP) and of proliferative activity of tumor cells were studied in male C3HA mice with transplanted hepatoma 22A. On day 4 after tumor transplantation, animals were subjected to a single sc inoculation with cyclophosphamide (CP: 150 mg/kg). CP was administered at 11 am, 5 pm, 11 pm, and 5 am. CP administration delayed the appearance and reduced the level of AFP. The most pronounced changes in AFP levels were observed after CP administration at 11 pm and at 5 am. CP produced mild inhibition of the proliferative activity of hepatoma 22A cells. (7 Refs) (In RUS)

49. CHANGES IN RENAL HANDLING OF PLATINUM IN CISPLATINUM-TREATED RATS FOLLOWING INDUCTION OF METABOLIC ACIDOSIS OR ALKALOSIS.

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Res Commun Chem Pathol Pharmacol; 36(2):273-285 1982

Manipulations of metabolic acid-base status were used in an attempt to modify the renal handling and toxicity of the anticancer drug cis-platinum. Rats were orally pretreated with either tap water (TW), ammonium chloride (AC), or sodium bicarbonate (SB) for 3 days prior to intraperitoneal administration of a high cisplatinum dose (7.5 mg/kg b.w.). Urine was collected daily for 4 days between drug dosing and killing of the animals. AC-pretreated rats did not exhibit the characteristic cisplatinum-induced diuresis and were unable to maintain an acid urinary pH following drug administration. AC rats had a significantly lower, and SB rats a significantly higher, urinary excretion of platinum than did TW rats. Platinum excretion was found to be correlated with urinary pH (r = 0.88) and not urinary volume (r = 0.30). The renal concentration of platinum was greater in AC animals than in SB or TW animals, but no significant difference was observed in liver or plasma concentrations between the groups. Both pretreated groups had equal percent of free vs bound platinum. Proteinuria was more severe in AC-pretreated rats, but histologic evidence of renal tubular damage was present in all the three groups. It is concluded that metabolic acidosis can seriously impair the renal handling of high dose cisplatinum but that metabolic alkalosis offers no evident advantages over nonpretreatment. (Author abstract) (19 Refs)

50. INTRACELLULAR LOCALIZATION OF RADIOACTIVELY LABELED MISONIDAZOLE IN EMT-6 TUMOR CELLS IN VITRO.

Miller GG, Ngan-Lee J, Chapman JD

Dept. Radiobiology, Cross Cancer Inst., 11560 Univ. Ave., Edmonton, Alberta, T6G 1Z2, Canada

Int J Radiat Oncol Biol Phys; 8(3/4):741-744 1982

The intracellular distribution of reduced misonidazole (MISO) was defined in EMT-6 tumor cells labeled under both hypoxic and aerobic conditions. The possibility that MISO cytotoxicity in hypoxic cells is a result of a selective elevated binding of the reduced drug to one or more cellular macromolecules was examined. No significant MISO uptake was observed in aerated EMT-6 cells. Under hypoxic conditions, incorporation of MISO was a linear function of the incubation time, following a brief initial lag period. Of the total acid-precipitable radioactivity, 78-86% was associated with the cytoplasm, while the remaining 14-22% was bound to the nuclear fraction. Approx 2% of MISO was associated with cell membranes. Cells labeled for 3 hr in the absence of O2 incorporated the drug greater than 55x, compared to cells labeled for the same period in 95% air-5% CO2. Binding to intracellular macromolecules did not demonstrate significant differences within fractions. The label was bound to the acid soluble cell fraction (77%), RNA (17%), DNA (1%), and lipid (4%). Only 1% of the radioactivity was bound to residual high mol wt protein. (24 Refs)

51. INHIBITION OF METABOLISM-MEDIATED CYTOTOXICITY BY 1,1-DISUBSTITUTED HYDRAZINES IN MOUSE MASTOCYTOMA CELLS (LINE P815).

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Dept. Biochemistry, Univ. Texas Health Science Center at Dallas, Dallas, TX, 75235

Adv Exp Med Biol; 136(partB):1067-1075 1982

Ability of N-aminopiperidine (NAP) to inhibit the cytotoxicity of cyclophosphamide (CPA) was studied using a hepatocyte/mastocytoma system. Male Sprague-Dawley CD rats (80-100 g body wt) were used. Hepatocytes (HC) were isolated from rat liver by collagenase/hyaluronidase digestion. When CPA was incubated with freshly isolated HC from phenobarbital-treated rats, a marked decrease in the number of viable P815 cells after 55 hr in culture was observed as the concentration of CPA increased; at CPA concentration of 0.27 mg/ml the viable cell number was only 6% of that present in the control cultures. No toxicity to the P815 cells could be detected even at the highest concentration of CPA used when HC were omitted from the incubation mixture. The pre-incubation of HC with 4.2 milliM NAP, followed by incubation with different concentrations of CPA resulted in a significant change in the dose-response curve for the toxicity of activated CPA to P815 cell. At all concentrations of CPA used NAP reduced the inhibition of P815 cells growth by approx 60%. Results presented indicate that in the case of 1,1-disubstituted hydrazines a correlation between the extent of complex formation with cytochrome P-450 observed in microsomal suspension and the degree of inhibition of the metabolite-mediated cytotoxicity of CPA exists. The ability of NAP to inhibit the CPA metabolite toxicity of the P815 cells was significantly reduced when HC from untreated or 5,6-benzoflavone-treated rats were used as the activating component in the system. (19 Refs)

52. INHIBITION OF ANTERIOR PITUITARY CYCLIC AMP PHOSPHODIESTERASE BY COLCHICINE AND VINBLASTINE.

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FEBS Lett; 141(1):25-28 1982

The inhibition of the anterior pituitary cyclic adenosine monophosphate phosphodiesterase (cAMP) by the microtubule inhibitors colchicine (COL) and vinblastine (VBL) was observed studying the possible role of the microtubules in the hormone secretion. Both alkaloids led to a significant increases in pituitary cAMP concentration as did theophylline and prostaglandin E2 that were included as positive controls. No effect of either COL (10(-3) M) or VBL (10(-4) M) upon pituitary adenylate cyclase activity was seen although prostaglandin E2 (10(-6) M) and sodium fluoride (10(-2) M) led to 2-and 4xX stimulations of the enzyme. In contrast, both alkaloids led to a concentration-dependent inhibition of the pituitary cAMP phosphodiesterase with about half-maximal effect being seen at 10(-3) M for both COL and VBL. The COL effect was seen in the presence or absence of divalent calcium (50 uM). Lumicolchicine, produced from colchicine by UV irradiation at 366 nanometers, was equipotent with COL in these studies. (16 Refs)

53. REVERSAL BY ISAXONINE OF THE INHIBITORY EFFECT OF VINCRISTINE ON THE GROWTH OF NEURITES IN CULTURES.

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Nouv Presse Med; 11(16):1233-1237 1982

It has been previously demonstrated that isaxonine increases neurite elongation of dorsal root ganglia in vitro. In purpose to demonstrate that this effect results of an action at the level of the cellular cytoskeleton, we have studied effects of isaxonine on neurite elongation inhibited by vincristine sulfate which is known to bind specifically on tubulin and consequently perturb microtubule assembly. Neurite elongation of dorsal root ganglia cultivated with vincristine (0.5 or 10-10M) is compared to neurite elongation of ganglia cultivated with vincristine plus isaxonine (10 7-10 1M). Results show that isaxonine prevents, at least partially, the effect of vincristine. The protective effect observed in vivo in the rat and in the human seems to indicate that isaxonine acts at the level of microtubules of nerve fiber. (Author abstract) (12 Refs) (In FRE)

54. HIGHER RESISTANCE OF GERM FREE MICE TO DIANHYDRODULCITOL, A LYMPHOTROPIC CYTOSTATIC AGENT.

Anderlik P, Szeri I, Banos Z, Wessely M, Radnai B

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Acta Microbiol Acad Sci Hung; 29(1):33-40 1982

Response to dianhydrodulcitol (DAD) was studied in 5-6-wk old germ free (GF), specific pathogen free (SPF), and conventional (CV) C3H mice of both sexes. In Experiment I, GF, SPF, and CV mice were treated with a 15 mg/kg DAD dose. In Experiment II, GF and SPF mice were treated with DAD in doses of 12, 15, or 18 mg/kg, and in Experiment III, GF and SPF mice received DAD in a dose of 15 mg/kg. In Experiment I, 15 mg/kg DAD caused no death in GF mice, while the mortality rate in SPF and CV mice was 50% and 80%, respectively, as registered on day 5 to 6 following treatment. Severe lymphoid atrophy was observed in mice that died on day 5 and 6. Mice surviving DAD treatment displayed lymphoid regeneration by day 21; the regeneration was almost equal in all groups of animals. In Experiment II, a 12 mg/kg DAD dose caused no death in GF mice; the mortality rate was under 10% and 30% after 15 mg/kg and 18 mg/kg DAD, respectively. In SPF the same dosages caused death in 10, 50, and 70% of animals, respectively. Mice in the SPF-DAD group died on day 5 to day 6, while those in the GF-DAD group died between day 5 and 10. No significant differences were observed between the data for the lymphoid organs of the GF-DAD and SPF-DAD groups with respect to the DAD doses. Experiment III was performed to study the effect of DAD on the gastrointestinal tract in GF and SPF mice. No toxic signs attributable to DAD were observed in the GF and SPF mice sacrificed immediately after DAD treatment (day 0). Significant differences were observed in the changes between the two groups of animals which died or were sacrified later. Necrosis of the mucosa and inflammatory infiltration were more expressed in SPF than in GF mice sacrificed on day 3. (13 Refs)

55. METABOLIC ACTIVATION OF ADRIAMYCIN BY NADPH-CYTOCHROME P-450 REDUCTASE, RAT LIVER AND HEART MICROSOMES AND COVALENT PROTEIN BINDING OF METABOLITES.

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Adv Exp Med Biol; 136(partA):471-485 1982

NADPH-dependent covalent binding of adriamycin-metabolites to bovine serum albumin and microsomal proteins in an aerobic in vitro-system with isolated NADPH-cytochrome P-450 reductase, rat liver, and rat heart microsomes, respectively, is reported. The covalent binding was revealed by means of spectrophotometric identification of the anthracycline moiety of the covalently bound adriamycin-metabolites. Based on this study and others, a model for the mechanism of antineoplastic, myelosuppressive, and cardiotoxic action of adriamycin, respectively, was proposed. Two reactive intermediates are generated in a cyclic process of bioreductive activation of adriamycin and spontaneous reoxidation; semiquinone radicals of adriamycin and superoxide radicals. NADPH and oxygen are consumed at the same time. Superoxide radicals formed by reoxidation and other reactive oxygen-species generated could be responsible for the destruction of intracellular macromolecules. The semiquinone radicals of adriamycin formed by bioreductive activation are metabolized to 7-deoxy-adriamycin-aglycone. The concomitant depletion of soluble sulfhydryls like glutathione may lead to further toxic effects. The results suggest covalent protein binding of adriamycin-semiquinone radicals formed by NADPH-cytochrome P-450 reductase. Because covalent protein binding also occurred in rat heart microsomes, this biological effect may contribute to adriamycin-induced cardiotoxicity; this method of determining covalent binding of adriamycin-metabolites to cardiac protein may be a useful in vitro test system for the analyzing the cardiotoxicity of new antineoplastic anthracycline antibiotics. (37 Refs)

56. ARE CELLULAR KINETICS USEFUL IN ANTITUMOR CHEMOTHERAPY.

Cazap E
Catedra de Oncologia Facultad de Medicina, Universidad del Salvador, Buenos Aires, Argentina
Rev Latinoam Oncol Clin; 13(3):5-13 1981

The usefulness of cell cycle kinetics in chemotherapy is discussed. It is concluded that, although many therapeutic schemes are based on the knowledge of cellular kinetics, the clinician should not expect to use cell cycle kinetics alone to determine the treatment schedules or the optimal drug doses for chemotherapy. (no Refs) (In SPA)

57. EXPERIMENTAL STUDY OF THE EFFECT OF PROSPIDIN ON THE ULTRASTRUCTURE OF TUMOR CELLS.

Mandzhgaladze MV, Popov VL, Chernov VA
Lab. Experimental Tumor Chemotherapy, S. Ordzhonikidze All-Union Res. Chemicopharmaceutical Inst., Moscow, USSR
Biull Eksp Biol Med; 93(3):79-81 1982

The effect of the antineoplastic drug prospidin on the ultrastructure of tumor cells was studied in rats with transplanted sarcoma 45. The rats received either single ip injection of prospidin at max tolerance dose (MTD: 1,000 mg/kg), or 10 injections at a therapeutic dose (TD: 145 mg/kg/day). Animals were sacrificed 3-120 hr after prospidin administration, and tumor specimens were subjected to electron microscope examination. The first ultrastructural changes in the sarcoma 45 cells were observed 12-48 hr after prospidin at MTD and after 3-5 injections at TD. The changes included swelling of the mitochondria, partial reduction of the crypts, and enlargement of the tubules of the endoplasmic reticulum. After 6-8 injections at TD and 72-96 hr after administration at MTD, sarcoma 45 cells were characterized by vacuolization of the cytoplasm, dystrophy of the mitochondria, and changes of the shape and the structure of the cell nucleus. Necrosis of the cells of the peripheral zone of sarcoma 45 was observed 120 hr after MTD and 48 hr after the last injection at TD. (10 Refs) (In RUS)

58. ANTIGENIC DIFFERENCES BETWEEN A PRIMARY HAMSTER LYMPHOSARCOMA AND ITS LIVER METASTASES.

Sherbet GV, Lakshmi MS, Risely GP, Shah SA, Tindle ME
Cancer Res. Unit, Univ. Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, England
Experientia; 38(5):610-611 1982

An antiserum was raised in rabbits against a primary metastasizing lymphosarcoma (ML) of the hamster. This was made tumor-specific by absorption with normal hamster tissue extracts. Immunoglobulin-G was prepared and tested for its cytotoxicity towards cells derived from the primary tumor and its liver metastases. The ML-specific IgG was found to be 2-5x more cytotoxic for cells derived from the primary tumor compared to cells obtained from liver metastases. (Author abstract) (16 Refs)

59. IN VITRO AND IN VIVO CYTOTOXICITY INDUCED BY AN ATTENUATED SALMONELLA: RELATION TO BACTERIAL CARRIER STATE AND RESISTANCE TO TUMOUR GROWTH.

Ashley MP, Kotlarski I
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Aust J Exp Biol Med Sci; 60(1):1-21 1982

In vivo and in vitro parameters of tumor resistance were examined after immunization of mice with the attenuated 11RX strain of S enteritidis. During the bacterial carrier state produced by intraperitoneal (ip) or intravenous (iv) injection of 11RX the mice were resistant to ip tumor growth, could destroy ip injected 125I- or 131I-labeled tumor cells in vivo and had non-specifically cytotoxic peritoneal cells (PC) which could lyse 51Cr-labeled tumor cells in vitro. Most of the in vivo and in vitro cytotoxic activity could be attributed to activated macrophages. The predominantly local nature of 11RX-induced anti-tumor activity was indicated by the superiority of the ip route of infection for induction of tumor resistance and in vivo and in vitro cytotoxicity. After iv injection of 11RX, none of the anti-tumor effects outlasted the bacterial carrier state. However, after ip infection, a dichotomy was observed between in vitro and in vivo anti-tumor effects. In vitro PC cytotoxicity lasted only for the length of the 11RX carrier state (approx 30 days), whereas resistance to ip tumor growth lasted for 60 to 100 days and was correlated closely with cytotoxic activity measured in vivo. Possible reasons for this dichotomy are discussed. (Author abstract) (36 Refs)

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ANTITUMOR AND ANTIVIRAL AGENTS

Experimental Therapeutics, Toxicology, Pharmacology

SERIES CB20 No. 82/11 NOVEMBER, 1982

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ANTITUMOR AGENT EFFICACY IN VIVO

1. 1-BETA-D ARABINOFURANOSYLCYTOSINE CONJUGATE OF PHOSPHOLIPID AS POTENTIAL NEW ANTITUMOR PRODRUG (MEETING ABSTRACT).

Hong CI, MacCoss M, Ryu EK, West CR
Department of Neurosurgery, Roswell Park Memorial Institute, Buffalo, NY, 14263

Proc Am Assoc Cancer Res; 23:788 1982

Ara-CDP-L-dipalmitin (1-beta-D-Arabinofuranosylcytosine 5'-diphosphate-5'-L-1,2-dipalmitin) has been shown to have an increased efficacy relative to the parent ara-C in in vivo antitumor studies against L1210 lymphoid leukemia in mice. Thus, we have evaluated the conjugate further for its response against ip and ic implanted L1210 leukemia in mice. The conjugate was administered ip as a sonicated solution in 0.9% NaCl. In the treatment of ip implanted L1210 in C3D2F1/J mice, the effectiveness of ara-CDP-L-dipalmitin was relatively insensitive to the schedules used for a given total dose. A single, widely spaced (qd, 1, 5, 9) and 5-day continuous dose therapy at a total dose of 125 mg/kg showed ILS values of 228, 171, and 260%, respectively, while those of ara-C at the optimal doses

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were 13, 63, and 89%, respectively. The conjugate was also found to be effective against the advanced L1210 leukemia. When a total of 125 mg/kg of the conjugate was administered in a single as well as a 5 day consecutive dose schedule beginning 5 days after tumor implantation, the ILS observed were 143 and 121%, respectively. In the treatment of ic inoculated L1210 leukemic mice, both a single and 5-day continuous doses of a total of 250 mg/kg showed promising therapeutic results (ILS, 237 and 295%, respectively), while those of ara-C at the optimal doses were 44 and 72%, respectively. The conjugate was found to be less effective against ara-C resistant L1210 in mice than L1210 leukemia. (1 Ref)

2. ANTITUMOR ACTIVITY OF 5'-DEOXY-5'-SUBSTITUTED-5-FLUOROURIDINE DERIVATIVES (MEETING ABSTRACT).

Ajmera S, Danenberg PV
Department of Biochemistry and Comprehensive Cancer Center, University of Southern California, School of Medicine, Los Angeles, CA, 90033
Proc Am Assoc Cancer Res; 23:773 1982

There is good evidence that the anti-tumor activity of 5'-deoxy-5-fluorouridine (5'-dFUrd) depends on its cleavage to fluorouracil (FUra) by uridine phosphorylase. However, 5'-dFUrd is a relatively poor substrate for this enzyme. We synthesized a series of 5'-deoxy-5'-substituted-5-fluorouridines in an effort to obtain derivatives that might have improved substrate properties for uridine phosphorylase and thus possibly be better prodrugs of FUra than is 5'-dFUrd. The 5'-hydroxyl group of 5-fluorouridine (FUrd) was replaced with the following substituents: H (5'-dFUrd), OTs, OMs, F, Cl, Br, I, N3, NH2, and ONO2. The uM concentrations of these compounds required to inhibit growth of L1210 cells in culture by 50% were 3.65, 0.46, 0.32, 29, 3.4, 0.8, 5, 170, 8.7, and greater than 100, respectively. Preliminary evaluation of in vivo anti-tumor activity was carried out in L1210-bearing DBA/2 mice. Daily ip injections of each compound for 5 days at doses of 250 mg/kg resulted in the following percent increases in life span compared to untreated controls: 5'-dFUrd, 120; 5'-OMsdFUrd, 158; 5'-FdFUrd, 158; 5'-CldFUrd, 164; 5'-Brd FUrd, 134; 5'-IdFUrd, 124 (at 200 mg/kg); 5'-NH2dFUrd, 128. (1 Ref)

3. EFFECTS OF ACLACINOMYCIN-A ON MURINE LEUKEMIA.

Nara N, Miyamoto T, Hirashima K, Momoi H
1st Dept. Internal Medicine, Tokyo Medical and Dental Univ., 5-45, Yushima 1-Chome, Bunkyo-Ku, Tokyo 113, Japan
Blood; 60(1):188-193 1932

Effects of aclacinomycin-A (ACM) on leukemic cells and normal hematopoietic stem cells were studied for the purpose of evaluating the usefulness of this agent as an antileukemic agent. ACM suppressed not only leukemic colony-forming unit (LCFU) in the radiation-induced murine erythroleukemia, but also normal hematopoietic stem cells (CFU-S, CFU-C) in mice. However, LCFU was the most sensitive to ACM. After the administration of ACM at a dose of 5 mg/kg, LCFU was suppressed to 0.02 of the control on Day 3 and recovered within 5 days. Splenic CFU-S and CFU-C were suppressed to the nadirs on Day 2 and Day 1, respectively, and they recovered within 5 days. On the basis of the differences in the sensitivities to ACM and recovery patterns between LCFU and normal hematopoietic stem cells, ACM at a single dose of 5 mg/kg was administered every 3 days (total dose of 25 mg/kg) into leukemic mice, and the increase in mean lifespan obtained 113.9%. Effectiveness of ACM in the treatment of acute leukemia was discussed. (Author abstract) (16 Refs)

4. 5-ACETOXY-2(3'-ACETOXYPHENYL)-3-ETHYL-1-METHYL-1H INDENE: A NEW MAMMARY TUMOR INHIBITING COMPOUND.

Schneider MR, Von Angerer E, Schonenberger H
(c/o Schonenberger) Inst. Pharmacy, Univ. Regensburg, Universitatsstrasse 31, 8400 Regensburg, W. Germany
Eur J Med Chem Chim Ther; 17(3):245-248 1982

The antitumor agent 5-acetoxy-1(3'-acetoxyphenyl)-3-ethyl-methyl-1H-indene (5AC) was synthesized by cyclization from 3,4-bis(3'-methoxyphenyl)-3,4-hexanediol. 5AC exhibits marked affinity to cytoplasmic estrogen receptor. 5AC inhibited the growth of dimethylbenzanthracene-induced, hormone dependent, mammary carcinoma in the SD-rat. (12 Refs)

5. EFFECT OF 1-(2-CHLOROETHYL)-3-ISOBUTYL-3-(BETA-MALTOSYL)-1 NITROSOUREA ON EXPERIMENTAL TUMORS.

Akaike Y, Arai Y, Taguchi H, Satoh H
Microbiological Res. Lab., Tanabe Seiyaku Co., Ltd., 2-2-50 Kawagishi, Toda, Saitama-ken 335, Japan
Gan; 73(3):480-487 1982

The antitumor activity of 1-(2-chloroethyl)-3-isobutyl-3-(beta-maltosyl)-1 nitrosourea (TA-077), a novel water-soluble nitrosourea derivative, against leukemia L1210, Ehrlich carcinoma, sarcoma 180, Lewis lung carcinoma, Yoshida sarcoma, rat ascites hepatomas and Walker 256 carcinosarcoma was examined and compared with those of three reference nitrosourea antitumor agents, 1-(2-chloroethyl)-3-(beta-D-glucopyranosyl)-1 nitrosourea, 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2 chloroethyl)-1-nitrosourea hydrochloride and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea. TA-077 exhibited a broad antitumor spectrum against the above tumors. Among these four nitrosoureas, TA-077 produced the best therapeutic ratios (OD/ILS30) against leukemia L1210, irrespective of the administration route and schedule employed. The ratio obtained by consecutive treatment (ip) was superior to that by single administration, a unique characteristic of this novel nitrosourea agent. The inhibitory effect of TA-077 on the growth of non-syngeneic tumors (solid form) was also significant in all administration routes employed (ip, iv and po). Furthermore, TA-077 showed a marked life-prolonging effect on both early and advanced forms of Lewis lung carcinoma. (Author abstract) (19 Refs)

6. TOXICITY OF DIETHYLAMINORESERPINE TO A TRANSPLANTABLE TUMOR: THE SIGNIFICANCE OF THE PRESENCE OF HYPOXIC CELLS.

Lehnert S
Dept. Radiation Oncology, McGill Univ., Montreal, Quebec H36 1A4, Canada
Cancer Res; 42(8):3028-3032 1982

The survival of clonogenic cells from two transplantable mouse tumors has been measured following ip injection of diethylaminoreserpine (DL-152) to the tumor-bearing mouse. Reduction of surviving fraction was seen for both tumors following injection of the drug, minimal numbers of surviving cells being seen from 24 to 48 hr after injection. Greater cell kill was observed for the KHT fibrosarcoma (surviving fraction = 3 x 10(-2) at 48 hr) than for the EMT6 mammary carcinoma (surviving fraction = 2 x 10(-1) at 48 hr). Reduction in surviving fraction of the KHT tumor was already observed at 1 hr after injection of the drug, and survival at that time was reduced if tumor cells were acutely hypoxic prior to excision of the tumor. Results also indicated that chronically hypoxic radioresistant cells were more sensitive to the drug than were aerated cells. Significant reduction in surviving fraction was seen for doses of DL-152 as low as 5 mg/kg. Using KHT tumors growing as lung nodules, it was shown that toxicity of DL-152 was not apparent until 11 to 14 days after initiation of the tumor and that subsequent sensitivity of cells to DL-152 increased with increasing age of the lung tumor. Hypoxic cells were detectable in 10-day-old lung tumors, a time at which the tumors were still resistant to the toxic effects of DL-152. In vitro experiments using KHT cells in suspension showed that a high concentration of DL-152 was toxic to both hypoxic and aerated cells but that hypoxic cells were more sensitive to lower concentrations than were aerated cells. (Author abstract) (14 Refs)

7. RADIOBIOLOGICAL ANALYSIS OF ANTITUMOR EFFECT OF SARCOLYSINE.

Iarmonenko SP, Syrkin AB, Solenov VN
All-Union Cancer Res. Center, Moscow, USSR
Med Radiol (Mosk); 27(5):66 1982

Comparative antitumor effects of sarcolysine (SL) and irradiation were studied in (CBA x C57)F1 mice bearing transplanted tumors. The mice were subjected to single gamma irradiations (800 rads) or to single ip injections of SL (7 or 14 mg/kg). The SL at 7 and 14 mg/kg induced tumor growth inhibitions of 60.5% and 95.9%, respectively, compared with 34.6% and 39.5% after local and whole-body irradiation. The SL at 14 mg/kg or the whole-body irradiation produced severe leukopenia, compared with slight leukopenia after the SL at 7 mg/kg or the local irradiation. (no Refs) (In RUS)

8. ANTITUMOR EFFECT OF RNASES MODIFIED BY COVALENT BINDING WITH DEXTRAN M-AMINOBENZYLHYDROXYLMETHYL ETHER.

Kurinenko BM, Kladova MS, Penzikova GA, Oreshina MG, Bulgakova RSh
Dept. Microbiology, State Univ., Kazan, USSR
Antibiotiki; 27(5):336-341 1982

Antitumor activities of native RNAse and RNAse modified by covalent binding with dextran m-aminobenzylhydroxylmethyl ether (DMAE) were compared in random-bred albino rats inoculated with 7-day Ehrlich ascites carcinoma (EAC) or sarcoma 37. On day 2 after tumor transplantation, the mice received ip injection of pancreatic RNAse or of RNAse isolated from Actinomyces rimosus. Native pancreatic RNAse had no antitumor activity (inhibitions of growths of EAC and sarcoma 37 were 2.2% and 10.5%, respectively). The native RNAse from A rimosus provided a 15.3% inhibition of growth of EAC and a 25.7% inhibition of growth of sarcoma 37. Covalent binding with DMAE increased the antitumor activity of both pancreatic RNAse (14.4-29.2% inhibition of EAC and 27.3-40.7% inhibition of sarcoma 37) and RNAse from A rimosus (25.2-50.7% and 40.1-55.5% inhibition, respectively). The increased antitumor activities of the modified derivatives were correlated with their increased half-lives in the ascitic fluid (AF). The differences in biological activities of pancreatic RNAse and RNAse from A rimosus were associated with greater sensitivity of the pancreatic enzyme to AF inhibitors. (13 Refs) (In RUS)

9. TREATMENT OF HUMAN BRAIN TUMORS IN ATHYMIC MICE WITH AZIRIDINYLBENZOQUINONE (AZQ) (MEETING ABSTRACT).

Schold SC, Friedman HS, Bjornsson TD, Shand DG, Bigner DD
Duke University Medical Center, Durham, NC, 27710
Proc Am Assoc Cancer Res; 23:693 1982

We have used athymic mice to treat subcutaneous (sc) tumors derived from 3 established human brain tumor cell lines. Two of the lines, D-54 MG and U-251 MG, were derived from anaplastic gliomas, and one, TE-671, was derived from a medulloblastoma. D-54 MG and U-251 MG were treated in a 6th animal passage, while TE-671 was treated in a 7th. For treatment, 30 ul of a tumor suspension was injected into the right flank of recipient animals. When the median tumor volume exceeded 200 mm3, the animals were divided into treatment and control groups without significant differences in average tumor volume between groups. AZQ was administered intraperitoneally daily x5 at a dose of 6.75 mg/m(2)/injection. Average weight loss was 3.1% of the pre-treatment body weight. Preliminary pharmacokinetic data in non-tumor bearing animals indicated rapid disappearance of the parent compound from plasma. Tumor regression after treatment occurred in 4 of 10 animals bearing D-54 MG, 1 of 10 bearing U-251MG and 1 of 5 bearing TE-671. The ratio of average treated tumor volume to average control tumor volume (T/C) 1.5 weeks after treatment began was 0.32 for D-54 MG, 0.70 for U-251 MG, and 0.51 for TE-671. Median time to 1 cm3 tumor volume (5x the treatment volume) exceeded control times by 12.9 days in D-54 MG and 3.3 days in TE-671 (T-C). T/C and T-C figures were statistically significant at the 0.05 level, but the number of tumor regressions was significant only in D-54 MG. (no Refs)

10. MODIFICATION AND TRANSFORMATION OF TUMOR CELLS INTO ANAEROBIC CELLS AS A NEW PRINCIPLE OF CANCER CHEMOTHERAPY.

Petrovsky BV, Kogan AKh, Efuni SN, Chernov VA, Sinianskaia GP, Minakova SM, Demurov EA
I. M. Sechenov First Medical Inst., Moscow, USSR
Patol Fiziol Eksp Ter; (2):45-51 1982

To test the hypothesis that modification or transformation of air tolerant tumor cells into obligatory anaerobic cells can be used as a new method of cancer chemotherapy, random-bred mice bearing Ehrlich ascites carcinoma (EAC) or sarcoma 180, and random-bred rats bearing Jensen sarcoma (JS) were subjected to administration of sodium diethyldithiocarbamate (DEDTC: 0.25, 0.35, 0.5, 0.67, or 0.75 g/kg, ip or im). The LD50 of DEDTC after 1-4-day administration was 1.[illegible].925 g/kg. Chronic administration of DEDTC (0.3 g/kg, ip, for 10 days) produced a 54% inhibition of liver superoxide dismutase (SOD). DEDTC (0.5 g/kg, ip, for 10 days) increased the duration of survival of mice bearing EAC (36 days, compared with 27 days in nontreated controls). DEDTC at 0.75 and 0.67 g/kg produced a 35% and 28%, respectively, inhibition of JS. Inhibition of EAC and sarcoma 180 was correlated with activity of SOD. Additional hyperbaric oxygenation stimulated formation of superoxide anion radical and thus enhanced the antitumor effect of DEDTC. In vitro experiments showed that in the presence of oxygen, DEDTC caused the death of approx 90% of EAC cells, compared with death of approx 14% cells in the presence of nitrogen. (19 Refs) (In RUS)

ANTITUMOR AGENT EFFICACY IN VITRO

11. CELL CYCLE EFFECTS OF CC-1065 (MEETING ABSTRACT).

Bhuyan BK, Crampton SL, Adams EG
The Upjohn Company, Kalamazoo, MI, 49001
Proc Am Assoc Cancer Res; 23:802 1982

CC-1065 is a very potent antitumor agent which is lethal to B16 and CHO cells and to a variety of human tumors in clonogenic assay at less than 1 ng/ml. It is effective against L1210 leukemia and B16 melanoma at 1-50 ug/kg. CC-1065 binds to DNA in a non-intercalative manner in the minor groove. We report here the kinetics of inhibition of DNA synthesis and the cell-cycle effects of the drug. DNA synthesis was measured as H3-TdR (thymidine) incorporation into DNA at different times after 2-hr exposure to 1 or 5 ng/ml of CC-1065. At 1 ng/ml, % inhibition immediately after (0 hr) drug exposure, 4 hr, 19 hr, and 24 hr was 34, 10, 82, and 64% respectively. Similarly at 5 ng/ml, the % inhibition was minimum at 4 hr and maximum at 19 hr after drug exposure. Since cell progression studies showed a marked change in % S phase cells during this time, the DNA synthesis rate was recalculated at cpm/S phase cell. These results showed that % inhibition of DNA synthesis was minimum at 0 hr and gradually increased to maximum inhibition at 19 hr. Cell progression studies showed that 2-hr exposure to CC-1065 blocked cells predominantly in G2+M. At 5 ng/ml, cells also accumulated in S whereas at 1 ng/ml cells were temporarily slowed in S. This resulted in marked difference in phase distributions between cultures exposed to 1 or 5 ng/ml. To determine phase-specific toxicity, we started synchronous cultures either from mitotic cells (selectively harvested after colcemid block) or from elutriated phase fractions. The former cultures showed that cells in M were much more sensitive than cells in late G1/early S. However, cells in different phases obtained by elutriation seemed to be equally sensitive in all phases of the cell cycles. (1 Ref)

12. CYTOCIDAL AND BIOCHEMICAL EFFECTS OF 3'-DEAMINO-3'-MORPHOLINODAUNORUBICIN (MD) AND ADRIAMYCIN (ADR) IN HUMAN COLON CARCINOMA (HT-29) CELLS IN CULTURE (MEETING ABSTRACT).

Johnston JB, Lin AJ, Glazer RI
Laboratory of Medicinal Chemistry and Biology, National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:687 1982

A new semisynthetic anthracycline analog, MD, possesses greater antitumor activity than ADR against murine tumors in vivo. To assess its activity in HT-29 cells, lethality was quantitated by soft agar cloning and DNA and RNA synthesis was measured by incorporation of [3H]TdR (thymidine) and [3H]UR (uridine), respectively, in log phase cells following 2 and 24 hr drug exposure intervals. After 2 hr treatment of log phase cells with 10-6M ADR or MD, cell viability was reduced 99% and 75%, respectively, whereas after 24 hr of exposure, 10-7M MD or ADR reduced cell viability 99% and 40%, respectively. DNA synthesis was inhibited 75% and 95% after 2 hr of exposure to ADR and MD, respectively, and was inhibited to a comparable degree after 24 hr treatment with 10-7M drug. In contrast. RNA synthesis was inhibited 45% and 85% by 2 hr treatment with 10-6M ADR or MD, and 15% and 50% after 24 hr of exposure to 10-7M ADR or MD, respectively. Studies of drug uptake revealed a rapid influx of 10-6M MD with 95% of the peak intracellular concentration (67 pmoles/ug DNA) accumulating in 1 hr. In contrast, ADR was slowly taken up and achieved a maximum concentration of 7 pmoles/ug DNA in 2 hr. The efflux of MD was equally rapid with intracellular levels reduced to and reaching a plateau of 40% of its maximum concentration in 1 hr, while the efflux of ADR was only 10% after 1 hr. The transport properties of MD vs ADR appear to be related to its greater lipophilic properties. (no Refs)

13. IN VITRO COMPARISON OF THE CYTOTOXIC AND CYTOKINETIC EFFECTS OF ADRIAMYCIN (ADR) ACLACINOMYCIN (ACL) AND CARMINOMYCIN (CAR) (MEETING ABSTRACT).

Wheeler RH, Natale RB, Clauw D, Dhafir R
University of Michigan, Ann Arbor, MI, 48109
Proc Am Assoc Cancer Res; 23:680 1982

ADR has a wide spectrum of activity in human neoplasms. ACL and CAR are new anthracyclines in early human trials. We have used a Burkitt Lymphoma cell line (P3J) to compare the cytotoxic and cytokinetic effects of these agents. Cytotoxicity of the three agents is concentration x time dependent in a manner characteristic of non-phase specific agents. Cytokinetic effects were determined by flow cytometry and thymidine incorporation (TI) following a 1 hour exposure to concentrations producing an IC10 to IC100 with or without the addition of colchicine to assess delay in G1/S and G2/S progression. ADR produced G2/S accumulation and a dose dependent slowing of S phase transit. CAR produced G2/M accumulation with little S phase effect and no G1S block. ACL produced a G1/S block at all concentrations and marked slowing of S phase transit. At the IC50 CAR did not inhibit TI, ADR produced 25% inhibition and ACL 75% inhibition. These three anthracyclines produce different dose dependent cytokinetic effects which must be considered in combination drug protocol design. (no Refs)

14. QUANTITATIVE DOSE-RESPONSE RELATIONS FOR CHLOROETHYLNITROSOUREAS IN CELL CULTURE: EFFECTS OF CONCENTRATION, DURATION, TEMPERATURE AND STRUCTURE ON CYTOTOXICITY (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:640 1982

Observed effects of individual agents and treatment schedules have been compared using a dose function that is thought to represent the amount of ultimate active alkylating species, 2-chloroethylazohydroxide, formed during the period of exposure to the drug. This dose function considers terms for the rate of partitioning of drug into the cell, the rate and yield of active intermediate formation, and the duration of the exposure period and may, therefore, be determined for any initial drug concentration, length of exposure, or incubation temperature. Since a common active intermediate is thought to be formed from different chloroethylnitrosourea analogs, this term may be used to compare activity of different members of this class of drug. Data will be presented to show that cytotoxic activity of these agents, when compared to the amount of active intermediate formed, is not dependent on the initial dose or duration of exposure. The effects caused by variation of the temperature at which BCNU (carmustine) is incubated with P388 cells are found to be related to changes in the rate of conversion of BCNU to intermediate and no change in the sensitivity of cells to this drug were found in a 27 to 42 C range. Three other chloroethylnitrosoureas, CCNU (lomustine), PCNU and CNU (chloroethylnitrosourea), were found to have the same activity as BCNU. In contrast, chlorozotocin required a two-fold higher effective dose to produce the same toxic effect as the above four analogs. (no Refs)

15. GROWTH-INHIBITORY EFFECTS OF DL-ALPHA-DIFLUOROMETHYL ORNITHINE IN THE SPECTRUM OF HUMAN LUNG CARCINOMA CELLS IN CULTURE.

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Cancer Res; 42(8):3070-3073 1982

DL-alpha-Difluoromethyl ornithine (DFMO) is a new and specific inhibitor of the first step in polyamine biosynthesis. We recently reported that DFMO profoundly diminishes cell survival in a single culture line of human small-cell lung carcinoma (SCC). In the present study, we have extended this work to ascertain: (a) the effects of DFMO on the spectrum of cell growth for SCC in culture; and (b) how the response of SCC cells to DFMO compares to that for the other three major types of human lung cancer cells. SCC cells were found to have a unique response to DFMO among the types of lung cancer; exposure of eight separate lines to the drug, during the exponential growth phase, produced an initial inhibition of cell increase followed by a progressive and complete loss of cells from the cultures. There was a heterogeneous response pattern among the SCC lines in that the time of onset for cell loss ranged from 4 days to 4 wk. In marked contrast to SCC, two lines of human lung adenocarcinoma, one of squamous cell carcinoma and one of large cell undifferentiated carcinoma, had a more usual response to inhibition of polyamine biosynthesis. Despite a cessation of cell proliferation during DFMO treatment, no cell loss ensued overperiods up to 8 wk in these cultures. The above results with SCC and non-SCC cells suggested that the former could not live well in culture as a resting, nonproliferative cell. We further tested this hypothesis by exposing to DFMO stationary-phase 4-wk-old aggregates of cultured SCC cells, in which cell proliferation and cell loss are balanced; within 2 wk, the profound loss of cells was again manifest. We conclude that: (a) in culture, SCC cells, among human lung cancer types, have a unique sensitivity to inhibition of polyamine biosynthesis; (b) the heterogeneity for timing of SCC response to DFMO may have to be taken into account when investigating the therapeutic potential of the drug, DFMO; and (c) the biological differences between SCC and non-SCC cells in response to DFMO may provide a model system for establishing further the functional role of the polyamines. (Author abstract) (18 Refs)

16. EFFECTS OF STEROID SEX HORMONES AND ADRIAMYCIN ON HUMAN BLADDER CANCER CELLS IN CULTURE.

Yoshimoto J, Matsumura Y, Tanahashi T, Ohmori H, Tokiwa T, Sato J
Dept. Urology, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan
Acta Med Okayama; 36(1):61-66 1982

The effects of steroid sex hormones on the established cell lines derived from human urinary bladder cancer, T24 and from human transitional cell cancer of the urinary tract, 253J, were examined using the colony formation method. Of the seven kinds of steroid hormones tested, estradiol-17beta was intensively cytotoxic for both cells. The cytotoxic effect was depended on the dose and time of treatment. The combined effect of Adriamycin and estradiol-17beta on T24 cells could be recognized at low concentrations of Adriamycin (less than or equal to 10(-3) ug/ml) after exposure for 24 hr. (Author abstract) (12 Refs)

17. CYTOTOXICITIES OF MITOMYCIN C AND X RAYS TO AEROBIC AND HYPOXIC CELLS IN VITRO.

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Int J Radiat Oncol Biol Phys; 8(6):1035-1039 1982

Effect of combination therapy with mitomycin C and x-rays were examined in EMT6 mouse mammary tumor cells in exponential growth in vitro. Although treatment with mitomycin C was toxic, it did not alter the shoulder or slope of the radiation dose-response curve. Mitomycin C and radiation treatments separated by several hr produced the same cytotoxicities as simultaneous treatments. The cytotoxicities of mitomycin C and x-rays were additive and independent of the sequence of treatments or interval between treatments. (24 Refs)

18. IN VITRO CYTOTOXICITY OF VP 16 ON PRIMARY TUMOR AND METASTASIS OF LEWIS LUNG CARCINOMA.

D'Incalci M, Erba E, Vaghi M, Morasca L
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Eur J Cancer Clin Oncol; 18(4):377-380 1982

VP 16 activity was investigated on cells derived from primary tumor or metastases of Lewis lung carcinoma grown in vitro. After 24 hr exposure to VP 16 we found a marginal effect at 0.1 ug/ml, but at 1 and 10 ug/ml [3H]-TdR uptake was 37 and 85% less than controls for primary tumor and 43 and 83% for metastases; cell numbers dropped to 41 and 76% of controls for primary tumor and 30 and 68% for metastases. After 72 hr exposure VP 16 had a similar effect on cells of primary tumor or metastases, but a cytotoxic effect was already evident at 0.01 ug/ml and increased proportionally to the concentration reaching virtual complete cell killing at 1 ug/ml. This study suggests that the much greater in vivo sensitivity to VP 16 of metastases than primary tumor of Lewis lung carcinoma probably arises less from an intrinsically greater susceptibility of metastatic cells than from pharmacokinetic factors. (Author abstract) (11 Refs)

19. EFFECT OF SODIUM CIS-BETA-4-METHOXYBENZOYL-BETA-BROMACRYLATE (CYTEMBENA) ON HELA CELL KINETICS.

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Cancer Res; 42(8):3193-3195 1982

The treatment of HeLa cells with various concentrations of sodium beta-4-methoxybenzoyl-beta-bromacrylate (Cytembena) results in inhibition of growth and modification of cell cycle distribution. These phenomena were observed at concentrations between 7.5 x 10(-5) and 2.5 x 10(-5) M. The estimation of DNA content by flow cytometry showed an important shift in the distribution of cycling cells with a relative decrease of G0 + G1 cells and a striking accumulation of G2 + M cells. According to our experimental conditions, the blocking up in G2 + M is irreversible at 7.5 and 5 x 10(-5) M. (Author abstract) (10 Refs)

20. DIAZOKETONE AND CHLOROMETHYLKETONE ANALOGS OF METHOTREXATE AS POTENTIAL ANTITUMOR AGENTS.

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J Pharm Sci; 71(6):717-719 1982

The synthesis of 4-amino-4-deoxy-N10-methylpteroyl-(6-diazo-5-oxo)-L norleucine and 4-amino-4-deoxy-N10-methylpteroyl-(6-chloro-5-oxo)-L norleucine, analogs of methotrexate in which the gamma-carboxyl group is replaced by a diazoketone and a chloromethylketone, respectively, was carried out. The analogs inhibited the growth of leukemia L-1210 cells in culture by 50% at 4 x 10(-7) M and 2 x 10(-7) M, respectively and were effective inhibitors of the synthesis of thymidylate in L-1210 cells in vitro (I50 = 3 x 10(-6) M), exhibiting significant antifolate activity. The results demonstrated the feasibility of introducing chemically reactive groups at the gamma-position of pteroyl glutamates with retention of biological activity. However, in the systems investigated thus far, there was no evidence of covalent bond formation due to these reactive groups at the active sites of the enzymes. (Author abstract) (23 Refs)

21. HUMAN MAMMARY EPITHELIUM IN CULTURE (MEETING ABSTRACT).

Smith HS, Stampfer MR, Hackett AJ

Peralta Cancer Research Institute, Oakland, CA

In Vitro; 18(3,part2):319 1982

Our laboratory has developed techniques to culture human mammary epithelial cells from normal and malignant specimens. The mammary tissue is enzymatically digested to pure epithelial clusters which may be cryopreserved in multiple ampoules permitting repetition of experiments with cells from individual donors. Utilizing an enriched media plus cholera toxin, the epithelial cells grow rapidly in mass culture for 1-4 subcultures. By plating the cells with fibroblast feeder layers, a clonal assay was developed with plating efficiencies of 1-40%. Cellular morphology, ultrastructural markers, fibronectin display, and demonstration of mammary-specific (milk fat) antigen indicated that the growing cells were indeed mammary epithelium. Cells derived from tumor specimens were distinguished from those of non-tumorous origin by the presence of mammary tumor glycoprotein antigen. Utilizing the clonal assay, we have generated dose response curves for the chemotherapeutic drug, adriamycin, using cultures from breast carcinomas and nonmalignant tissues. We are able to detect heterogeneity in response to adriamycin among breast carcinoma cultures as well as among the nonmalignant specimens. In some cases (both normal and malignant) we also detected heterogeneity in response to the drug among subpopulations within a single specimen. (2 Refs)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

22. CROSS-RESISTANCE OF CULTURED MURINE LEUKEMIA VINCRISTINE-RESISTANT P388 CELLS TO VINBLASTINE, VINDESINE, AND BIS(N-ETHYLIDENE VINDESINE) DISULFIDE, DISULFATE.

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JNCI; 68(6):1023-1026 1982

Cultured P388 leukemia cells derived from vincristine (VCR)-resistant cell populations developed in vivo in (C57BL x DBA/2)F1 mice (P388/VCR) were cross-resistant to vinblastine (VLB), vindesine (VDS), and bis(N-ethylidene vindesine)disulfide, disulfate (bis-VDS). Cross-resistance was a function of concentration and time of exposure. Cultured P388/VCR cells were more sensitive to 6.1 x 10(-5) M bis-VDS than to 6.1 x 10(-5) M VDS or to 6.1 x 10(-5) M VLB. Cultured P388 cells derived from VCR-sensitive P388 leukemia passaged in vivo (P388/0) were significantly more sensitive to VDS and bis-VDS than to VLB. This degree of difference in sensitivity was also a function of concentration and time of exposure. (Author abstract) (32 Refs)

23. ESTABLISHMENT OF VINCRISTINE-RESISTANT AND VINDESINE-RESISTANT LINES OF MURINE LYMPHOBLASTS IN VITRO AND CHARACTERIZATION OF THEIR PATTERNS OF CROSS-RESISTANCE AND DRUG SENSITIVITIES.

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Cancer Chemother Pharmacol; 8(2):163-169 1982

The possible lack of cross responsiveness between vincristine (VCR) and vindesine (VDS) was investigated utilizing newly developed drug-resistant cell lines from L5178Y lymphoblasts. Cell lines resistant to either drug were easily established following a limited exposure to high drug concentrations of 200 nanog/ml. Resistant lines were similar to parental cells in terms of doubling time, cell cycle distribution, cell volume, modal chromosome number, and cellular DNA, RNA and protein contents. Cross resistance between VCR and VDS was not invariable and appeared to be dose dependent. Either partial or complete resistance was observed to other vinca alkaloids, to the anthracyclines, and to actinomycin D (ACT D). Full sensitivity was retained to methotrexate and 5-fluorouracil. Both the VCR-resistant and VDS-resistant lines exhibited comparable patterns of sensitivity or resistance to other antitumor drugs. The VDS-resistant line exhibited cross resistance to both ACT D and 4'-(9-acridinylamino)- methanesulfon-m-anisidine (mAMSA), while the VCR-resistant line showed only slight resistance to ACT D but full sensitivity to mAMSA. This suggests that mAMSA may be valuable in specifically overcoming resistance to VCR, suggesting that VDS may be valuable as second-line therapy in tumors equally responsive to the two vinca alkaloids. (32 Refs)

24. POTENTIATION OF CHEMOTHERAPY BY HYPOXIC CELL RADIATION SENSITIZERS. A REVIEW.

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Int J Radiat Oncol Biol Phys; 8(6):1029-1034 1982

Chemo-potentiation by radiosensitizers is reviewed. Misonidazole (MISO) and other sensitizers have been evaluated in combination with in vivo chemotherapy. In general MISO has been found to be equal or superior to metronidazole, Ro-05-9963, SR-2508, and SR-2555 when compared on an equimolar basis. Chemotherapeutic agents for which different sensitizer comparisons have been made in two or more studies include melphalan, cyclophosphamide (CYC), carmustine (BCNU), and lomustine. Many studies have shown the effect of MISO to be largest with small doses of the chemotherapeutic agent; MISO may not be dose modifying when used as a chemo-potentiator. Pharmacologic studies with BCNU and CYC have given opposing results. While the pharmacokinetics of BCNU appear unaltered by MISO, those of CYC may be affected. Chemopotentiation is not likely a consequence of the drug left in the cell at the time of treatment with the second agent, but rather is a result of the presence of damage inflicted on the cell by the pretreatment. The sensitizer interferes with the repair of damage caused by the chemotherapeutic agent. MISO interfered with the recovery of clonogenic cell survival after treatment with CYC while Ro-05-9963 did not. Altered pharmacokinetics, inhibition of damage repair, direct cell kill enhancement, as well as manifestation of the in vitro pre-incubation effect may be involved in chemo-potentiation by radiosensitizers. (64 Refs)

25. NITROSOUREA-MISONIDAZOLE COMBINATION CHEMOTHERAPY: EFFECT ON KHT SARCOMAS, MARROW STEM CELLS AND GUT.

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Br J Cancer; 45(6):835-842 1982

C3H/HeJ mice bearing im transplanted KHT sarcomas were treated with varying doses of either 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) or 2- *3-(2-chloroethyl)-3-nitrosoureido* -D-glucopyranose (chlorozotocin; CHLZ) as single agents or in combination with 1 mg/g of the chemical radiosensitizer, misonidazole (MISO). Using an in vivo-in vitro tumor-excision assay, the administration of MISO simultaneously with or 3 hr after low doses of BCNU (less than 20 mg/kg) was found to give a dose-modification factor (DMF) of approx 1.65 relative to BCNU alone. At higher doses of BCNU, there was less enhancement of cell kill. The DMF for tumor growth delay was likewise dependent on BCNU dose, continuously decreasing with increasing BCNU dose. In contrast, the anti-tumor activity of CHLZ, assessed by both clonogenic cell survival and tumor-growth delay, was not significantly enhanced by the addition of MISO. The enhancement of gastrointestinal toxicity and hematotoxicity by BCNU-MISO combinations was assessed by LD50/7 and CFU-S assays, respectively. MISO enhanced BCNU marrow toxicity by a factor of 1.2-1.3, while gut toxicity was enhanced by a factor of approx 1.2. (Author abstract) (22 Refs)

26. DIETARY INFLUENCE OF TYROSINE AND PHENYLALANINE ON THE RESPONSE OF B16 MELANOMA TO CARBIDOPA-LEVODOPA METHYL ESTER CHEMOTHERAPY.

Meadows GG, Pierson HF, Abdallah RM, Desai PR
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Cancer Res; 42(8):3056-3063 1982

The effect of dietary tyrosine and phenylalanine on survival of adult female C57BL/6 x DBA/2 F1 mice bearing ip slow-growing, moderately pigmented and fast-growing, highly pigmented B16 melanoma tumors was studied alone and in combination with carbidopa-levodopa methyl ester chemotherapy. These studies tested three different diets: a natural product diet containing 1.09% phenylalanine and 0.64% tyrosine (commercial diet); a chemically defined crystalline amino acid diet containing 0.6% phenylalanine and 0.3% tyrosine (purified diet); and a nutritionally deficient chemically defined diet containing 0.08% phenylalanine and 0.04% tyrosine (deficient diet). Mice received carbidopa (100 mg/kg) and levodopa methyl ester (1,000 mg/kg) ip daily for 12 days. The median survival of mice bearing the slow-growing tumor averaged 8 days longer than that of mice bearing the fast-growing tumor. Median survival increased by 42% (slow-growing tumor) and by 30% (fast-growing tumor) in mice maintained on the deficient diet. Drug treatment significantly increased survival in mice maintained on the purified and deficient diets but was relatively ineffective in mice maintained on the commercial diet regardless of the tumor growth characteristics. The largest increases in median survival of 61% (slow-growing tumor) and of 78% (fast-growing tumor) occurred in the treated mice maintained on the deficient diet. Plasma tyrosine and phenylalanine levels decreased by 33 and 21%, respectively, in mice maintained on the deficient diet and were unaffected by drug treatment. Tumors were 60% smaller in mice maintained on the deficient diet compared to mice maintained on the purified diet. Drug treatment resulted in decreased food intake and wt loss in all tumor-bearing dietary groups. Restricting food intake in untreated tumor-bearing mice to the amounts consumed by the drug treatment groups resulted in a parallel loss in body wt but no significant alteration in median survival. These data show that concomitant dietary tyrosine-phenylalanine restriction enhances the antitumor activity of carbidopa-levodopa methyl ester against B16 melanoma. (Author abstract) (51 Refs)

27. CELL KILLING BY VARIOUS NITROSOUREAS AND THE POTENTIATING EFFECT OF CAFFEINE.

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Mutat Res; 94(2):237-244 1982

The extent of sensitization by caffeine of cell killing by carmustine (BNCU), lomustine (CCNU), chlorozotocin (CHLZ), N-ethyl-N-nitrosourea (ENU), N-methyl-N-nitrosourea (MNU), and 1,3-bis(trans-4-hydroxycyclohexyl)-1-nitrosourea (BHCNU) was investigated in Chinese hamster bone marrow cells (650A cells). When killing of 650A cells by the various nitrosoureas was determined as a function of amount of drug decomposed in the exposure interval, the loss of colony-forming ability varied considerably with the nitrosourea used, although all agents gave a shouldered response. Cell killing by BCNU and CCNU was highest, followed by CHLZ then BHCNU; ENU was much less toxic than any of the other agents. The mean lethal dose (D0) values for BCNU, CCNU, CHLZ, and BHCNU ranged between 1.8 and 6 uM, whereas that for ENU was 2,100 uM. For all drugs, the extrapolation number, n, was between 2-7 except for BHCNU, for which it was 29. Caffeine, at a nontoxic dose in untreated cells (1 milliM), reduced the survival of cells after treatment with ENU, BCNU, CCNU, or CHLZ. Caffeine reduced the shoulder and the D0, potentiating cell killing with ENU the most, with CHLZ the least. However, after treatment with BHCNU, the presence or absence of caffeine had no effect on the colony-forming ability of the cells. Results indicated that potentiation of cell killing by caffeine is based on the reaction of a drug with the cellular DNA. (31 Refs)

28. ENHANCED UPTAKE OF ACTINOMYCIN D IN THE DOG KIDNEY BY SIMULTANEOUS INJECTION OF DEGRADABLE STARCH MICROSPHERES INTO THE RENAL ARTERY.

Tuma RF, Forsberg JO, Agerup B
Dept. Physiology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Cancer; 50(1):1-8 1982

Tritiated Actinomycin D and degradable starch microspheres were simultaneously injected into a renal artery in dogs. The spheres functioned to mechanically retard the washout of the drug from the kidney microcirculation. Degradation of the spheres by endogenous amylase resulted in the reestablishment of normal kidney blood flow within an hour after injection. Twenty-three percent of the total amount of drug injected was retained in the kidney 1 hr after injection of the drug-sphere combination. When the same amount of the drug alone was selectively injected into a renal artery or given intravenously, 9% and 1.3% of the injected dose, respectively, was found in the kidney tissue 1 hr after injection. This procedure may be of benefit in the treatment of solid tumors, where the therapeutic ratio may be increased because of higher drug retention in the tumor tissue with a decreased availability of the drug for other sensitive tissues. (Author abstract) (12 Refs)

29. SYNERGISTIC CYTOTOXICITY INDUCED BY SODIUM BUTYRATE IN COMBINATION WITH CHEMOTHERAPEUTIC AGENTS IN CELL CULTURE (MEETING ABSTRACT).

Vu VT, Moy BC, Pinsky SD, Schein PS, Tew KD
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Proc Am Assoc Cancer Res; 23:751 1982

In the present study, the effect of sodium butyrate (SB) in combination with chemotherapeutic agents was evaluated in HeLa S3 cells. The cytotoxic effect was determined by a soft agar CFU-C (colony forming units in culture) assay with plating efficiencies of 10%. Pretreatment of SB (5mM, 22 hr) produced no toxicity per se but enhanced synergistically the cytotoxicity of nitrosoureas. In combination with chlorozotocin (CLZ) it produced a reduction of cell survival from 47% to 22% at 50uM CLZ and from 35% to 11% at 100uM. The effect of SB combined with nitrogen mustards was only additive. The cell survival was reduced from 31% to 21% and from 20% to 10% at 25 and 50uM of phosphoramide mustard, respectively. The lack of synergism may be due to the absence of carbamoylating properties of nitrogen mustards. The exact mechanism(s) by which SB enhances the cytotoxicity of alkylating agents is presently not understood. However, there is evidence that it could interfere with protein post-translational modification processes. Initial studies showed that SB alone or in combination with alkylating agents did not affect the phosphorylation activity of total nuclear protein nor the nuclear protein matrix by using an in vitro system of isolated nuclei and gamma-32P-ATP. Protein phosphorylation studies using permeable cells are currently under investigation. (no Refs)

30. SYNERGISTIC ACTION OF ACIVICIN AND ACTINOMYCIN ON HEPATOMA GROWTH AND NUCLEOTIDE METABOLISM (MEETING ABSTRACT).

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Laboratory for Experimental Oncology, Indiana University School of Medicine, Indianapolis, IN, 46223
Proc Am Assoc Cancer Res; 23:738 1982

Hepatoma 3924A cells were grown in McCoy's 5A medium and were treated with the drugs for 7 days; survival was measured by colony counts. With 0.5 uM acivicin, 45% survival was observed, with 0.01 uM actinomycin, 90%, but with the 2 drugs together there was a synergistic effect of 15% survival. Acivicin decreased the concentrations of GTP (guanosine triphosphate) and CTP (cytidine triphosphate) to 56 and 46% and elevated that of UTP (uridine triphosphate) to 152% of the controls. Only a combination of cytidine (1 mM), deoxycytidine (0.01 mM) and guanosine (0.01 mM) could completely protect tumor cells from acivicin (0.1 mM). The results are consistent with inhibition of both GTP and CTP synthetases. Adding actinomycin to acivicin in the medium increased the content of GTP, 1.9-, CTP, 4.2-and UTP, 1.6-fold over that in the cells treated with acivicin alone. The accumulation of GTP and CTP was attributed to inhibition by actinomycin of RNA polymerase activity. Hepatoma 3924A was transplanted sc in ACI/N rats and next day we started ip injection of acivicin (1 inj/week, 24 mg/kg) or actinomycin (5 ug/kg, 4 x per week). At 14 days in each group treated with acivicin or with actinomycin there was an inhibition of tumor size to 58% of control. Combination of the treatment schedule of acivicin and actinomycin together yielded a synergistic inhibition of tumor size to 16% of controls. (2 Refs)

31. COMBINATIONS OF CCNU AND RADIOSENSITIZERS IN VIVO: MISONIDAZOLE AND BENZONIDAZOLE (MEETING ABSTRACT).

Siemann DW
Experimental Therapeutics Division, University of Rochester Cancer Center, Rochester, NY, 14642
Proc Am Assoc Cancer Res; 23:644 1982

In a number of different mouse model systems the radiosensitizer misonidazole (MISO) has been shown to enhance the antitumor activity of CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) to a greater extent than the hematologic or gastrointestinal toxicities. The present studies compared the potential therapeutic benefit of combining MISO (partition coefficient, pc-0.43) or BENZO (benznidazole, pc-8.5) in KHT sarcoma-bearing C3H mice. Both sensitizers were administered intraperitoneally and given either 30 min before (BENZO) or simultaneously with (MISO) the chemotherapeutic agent. Survival of clonogenic tumor cells assessed 24 hr after treatment or in situ tumor growth delay were used as assays of tumor response. Normal tissue toxicity was determined using the LD50/30 endpoint. In the KHT sarcoma, when combined with CCNU, doses of 2.5mmoles/kg MISO or 0.3mmoles/kg BENZO were found to yield approx equivalent increases in both the tumor effect and normal tissue toxicity. Both sensitizers therefore led to a therapeutic benefit. However, although an approx 10 fold lower dose of the more lipophylic sensitizer BENZO proved to be as effective as MISO at enhancing the tumorcidal effects of CCNU, this dose reduction did not translate directly into a greater therapeutic gain for BENZO. (no Refs)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

32. LETHAL NEPHROTOXICITY AND HEMATOLOGIC TOXICITY OF CIS-DIAMMINEDICHLOROPLATINUM AMELIORATED BY OPTIMAL CIRCADIAN TIMING AND HYDRATION.

Levi FA, Hrushesky WJ, Halberg F, Langevin TR, Haus E, Kennedy BJ
Section Medical Oncology, Univ. Minnesota Health Sciences, PO Box 286, Minneapolis, MN, 55455
Eur J Cancer Clin Oncol; 18(5):471-477 1982

Three hundred and forty-one female F344 (Fischer) rats were kept in light for 8 hr alternating with darkness for 16 hr; some were observed for survival for 21 days, while others were killed for blood sampling 4.5 days after a single intraperitoneal (ip) injection of 11 mg/kg cis-diamminedichloroplatinum (cis-DDP). cis-DDP was administered with or without concomitant ip saline load at one of six equispaced circadian stages. This high dose of cis-DDP resulted in marked lethal and renal toxicity, but in a moderate bone marrow suppression. Blood urea nitrogen (BUN), circulating total white blood cell counts (WBC) and survival times revealed statistically significant circadian rhythms of drug toxicity (p less than 0.03). Optimal tolerance for cis-DDP gauged by these three variables resulted from drug administration in the second half of the dark span. Renal tolerance for cis-DDP gauged by BUN was improved two-fold by appropriate drug timing. This benefit from drug timing alone was further improved two-fold if hydration and cis-DDP were given at the optimal circadian stage. Hydration-induced amelioration of cis-DDP nephrotoxicity requires time qualification of both hydration and cis-DDP. (Author abstract) (34 Refs)

33. MODULATION OF CIS-PLATINUM RENAL TOXICITY BY THE RADIOPROTECTIVE AGENT WR 2721.

Jordan SW, Yuhas JM, Glick J
Dept. Pathology, Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131
Exp Mol Pathol; 36(3):297-305 1982

Pretreatment with the radioprotective thiol compound WR 2721 resulted in amelioration of renal histologic damage induced at 5 and 31 days in rats by a single exposure to cis-dichlorodiammineplatinum II (cis-Pt), an anticancer agent. Renal histopathologic changes 5 days after exposure consisted of tubular epithelial necrosis at the corticomedullary junction, while after longer time intervals, nuclear hypertrophy, anisonucleosis, and diminished tubular diameters were evident. The degree of histologic change at 5 days was inversely correlated with the amount of WR 2721 administered. At 31 days after a single cis-Pt dose following pretreatment with 200 mg/kg WR 2721, the dose reduction factor (treated/control) was 1.5-1.6. (Author abstract) (12 Refs)

34. ZINC-INDUCED RESISTANCE TO ALKYLATING AGENT TOXICITY.

Tobey RA, Enger MD, Griffith JK, Hildebrand CE
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Cancer Res; 42(8):2980-2984 1982

Suspension cultures of line CHO Chinese hamster cells and three derived cadmium-resistant variants were exposed to 100 uM ZnCl2 prior to treatment with the alkylating agent, melphalan, and cytotoxicity was then determined by measuring colony-forming ability. A 10-fold or greater enhancement in survival of all zinc-pretreated cultures subsequently exposed to melphalan was observed which was unrelated to metallothionein induction capacity. Although the maximum achievable protection afforded by zinc occurred in cultures receiving 100 uM ZnCl2, concentrations of zinc only slightly in excess of levels found in human serum were shown to provide a 4.5-fold enhancement of protection, indicating that the phenomenon can also be induced at physiologically reasonable levels. These results suggest the existence of a novel zinc-inducible mechanism which protects cells against the toxic effects of alkylating agents. (Author abstract) (29 Refs)

35. THE EFFECT OF CYTOTOXIC AGENTS 5-FLUOROURACIL (5-FU) AND ARABINOSIDE-CYTOSINE (ARA-C) ON THE SMALL INTESTINAL ENZYMES AND MORPHOLOGY IN THE RAT (MEETING ABSTRACT).

Arvanitakis C, Nakos V, Tziolas J, Mokka F, Fountzilas G, Tzioufa V, Tourkantonis A
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Gastroenterology; 82(5,part2):1010 1982

Cytotoxic agents influence the mitotic activity and cellular turnover of various biological systems. We studied the effect of 5-FU and ARA-C on small intestinal disaccharidases and dipeptidases and histology in the rat. Following the IP administration of 5-FU (15 mg/kg) and ARA-C (13 mg/kg), the animals were killed on the 1st, 3rd and 6th day, biopsies were examined by light microscopy and mucosal homogenates assayed for the disaccharidases sucrase, maltase, lactase and dipeptidases leucyl-aminopeptidase (LNA), glycyl-glycinase (Gly-Gly) and leucyl-glycinase (Leu-Gly). No significant difference in the specific enzymatic activity was detected between the control, 5-FU and ARA-C on the 1st day of the experiment. Disaccharidases and dipeptidases activity was markedly decreased in the 5-FU and ARA-C group, as compared with the controls. With the exception of LNA, the rest of the enzymes returned to normal on the 6th day. Histological analysis of the small intestinal mucosa did not show any significant changes. Conclusion: 5-FU and ARA-C inhibit small intestinal enzymes on the 3rd day. This inhibition is reversible on the 6th day which indicates that cell renewal may occur after a single dose of cytotoxic agents. (no Refs)

36. SELECTIVE RESCUE OF 5-FLUOROURACIL (FU) - INDUCED HOST TOXICITY WITH DELAYED ADMINISTRATION OF URIDINE (UR) (MEETING ABSTRACT).

Martin DS, Stolfi RL, Sawyer RC, Spiegelman S, Young CW
Catholic Medical Center, Woodhaven, NY, 11421
Proc Am Assoc Cancer Res; 23:739 1982

Because of the association between the incorporation of FU into RNA and cytotoxicity, UR was examined for potential selective reduction of host toxicity. CD2F1 male mice (tumor-free, or bearing advanced Colon tumor 26) were used. Two UR schedules (each beginning 2 hrs after FU) have been successful: 1) UR at 800 mg/kg q2hx3 followed 18 hrs later by UR at 800 mg/kg q2hx4; or, 2) Two doses of UR 3500 mg/kg separated by an 18 hr interval. With UR 3500 mg/kg x 2 the LD50 for a single dose of FU in tumor-free mice was increased 68% from 190 mg/kg to 320 mg/kg. WBC levels were depressed 67% after a single dose of FU at 200 mg/kg, whereas WBC were depressed by only 39% when the same dose of FU was followed by UR-Rescue. In tumor-bearing mice UR-

Rescue reduced FU-induced host toxicity without significant loss of antitumor activity. Even more striking results were obtained with a combination containing PALA, N-(Phosphonacetyl)-L-aspartate (200 mg/kg), and MMPR, 6-Methylmercaptopurine Riboside (25 mg/kg), administered 24 hrs before FU. In this drug combination, the maximum tolerated dose of FU is 40 mg/kg on a weekly schedule. With UR-Rescue, FU can be doubled to 80 mg/kg without increased toxicity resulting in significantly improved antitumor activity. (no Refs)

37. REDUCTION OF LETHAL TOXICITY OF CHLOROETHYLNITROSOUREAS BY SUGAR ALCOHOLS WITHOUT LOSS OF ANTITUMOR ACTIVITY.

Tashiro T, Inaba M, Sakurai Y
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Cancer Chemother Pharmacol; 8(2):183-188 1982

The effects of several sugar alcohols, including mannitol, on the lethal toxicity of 1-(2-chloroethyl)-3-(methyl alpha-D-glucopyranos-6-yl)-1-nitrosourea (MCNU) was investigated. While CD2F1 mice given 50 mg MCNU/kg ip died from toxicity 7-10 days after treatment, pretreatment with sugar alcohols (3,000 mg/kg) one minute or less before MCNU prevented death from acute toxicity. Both po and ip administration of sugar alcohols was effective, although po less so. Mannitol was more protective than sorbitol, especially at lower doses. Mannitol-treated animals showed a faster recovery from myelosuppression compared to animals treated with MCNU only. Sugar alcohol protection did not diminish the antitumor effect of MCNU. With P388 mouse leukemia, neither the growth inhibition of MCNU nor the percentage increase in the lifespan of tumor-bearing mice at the minimum effective dose of MCNU were altered. Mannitol also did not diminish the antitumor effect of MCNU against sc-implanted Lewis lung carcinoma. Sugar alcohols apparently play a role in recovery from the toxic effects of MCNU. (6 Refs)

38. EFFECT OF ACRYLAMIDE ON ACETYLCHOLINESTERASE AND NEURON SPECIFIC ENOLASE ACTIVITY IN MOUSE NEUROBLASTOMA CELLS (MEETING ABSTRACT).

Krause D, Nardone RM
Catholic University of America, Washington, DC, 20064
In Vitro; 18(3,part2):325 1982

A study of the effect of three acrylamides on mouse neuroblastoma cells (NIE-115) and chick brain cell aggregates has revealed a good correlation between the in vivo and the in vitro toxicity ranking of these neurotoxic chemicals. This avenue of investigation has been expanded to include the effect of acrylamide on neuronal endpoints (acetylcholinesterase (AChe) and neurospecific enolase activity) and non-neuronal endpoints (cell survival, proliferation, and enolase activity) in proliferating and dibutyryl c-AMP differentiated NIE-115 cells. Forty-eight hour survival and proliferation of the cells showed a graded dose response. A concentration of 0.01 mM reduced proliferation rate by 10% while 5 mM was completely inhibitory. The AChE activity was unaffected (120 umol product formed/min/mg protein). The AChE activity level was six-fold higher in the differentiated cells and was unaffected by the doses of acrylamide which were used. On the other hand, when survival was used as an endpoint, the differentiated cells showed increased sensitivity; a dose of 3 mM for 48 h was lethal to the culture. Exposure to 0.5 mM for 48 h resulted in a 50% reduction in the activity of neuron-specific enolase while the activity of non-neuron specific enolase was unaffected. (no Refs)

39. THE IN VITRO TERATOGENICITY OF CYCLOPHOSPHAMIDE IN RAT EMBRYOS.

Greenaway JC, Fantel AG, Shepard TH, Juchau MR
Central Lab. for Human Embryology, Dept. Pediatrics, RD-20, Univ. Washington, Seattle, WA, 98195
Teratology; 25(3):335-343 1982

Embryonic defects induced by cyclophosphamide (CP) in rat embryos in vitro and in vivo were compared. Characteristic malformations were induced by growing Day 10 embryos in culture containing CP, hepatic microsomal fraction (S-9), and cofactors for monooxygenation. Abnormalities included cephalic defects and anomalies of the limb bud, tail, and mandibular arch; decrements were seen in crown-rump length, somite number, and protein content. Histologically, embryos exposed to CP in vivo were not distinguishable from those exposed in vitro. The av protein content of embryos exposed in vitro to a constant level of CP (25 ug/ml) decreased with increasing concentrations of S-9 from animals pretreated with polychlorinated biphenyls (PCB: Aroclor 1254). Malformation incidence was more sensitive than av protein content to changes in S-9 concentration. S-9 prepared from phenobarbital-pretreated rats produced a high incidence of malformations in embryos exposed to CP and cofactors, while use of S-9 from methylcholanthrene-pretreated animals and the same concentration of CP and cofactors did not result in malformations. Metyrapone and carbon monoxide effectively reduced teratogenic activity generated with S-9 from PCB-pretreated rats. Addition of metyrapone significantly increased embryo growth relative to that seen after treatment with CP plus activation but no metyrapone. The presence of 10% CO and 10% O2 also diminished the teratogenic effect but to a lesser extent than metyrapone. These findings support the idea that teratogenicity of CP is dependent upon one or more maternal P450 monooxygenase systems. (23 Refs)

40. ENHANCEMENT OF THE TOXIC EFFECT OF ENDOXAN IN THE RAT AFTER PRETREATMENT WITH BRAIN HOMOGENATES.

Ivankovic S, Frank N, Filipovic N, Haupt P, Wiessler M
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Arch Geschwulstforsch; 52(5):355-361 1982

The effects of brain tissue on the toxicity and therapeutic effect of endoxan (END) were studied in 2-mo-old male and female rats of strain BD IX. Rats were injected ip with 50 or 150 mg END/kg body wt after incubation of END with homogenates of rat brain tissue. For comparison of the effects of liver tissue on END, other rats were injected with 150 or 250 mg END/kg after incubation of END with homogenates of rat liver tissue. Control rats were injected with brain or liver tissue. Of the rats treated with END incubated with brain tissue, 18/18 receiving 150 mg/kg and 6/8 receiving 50 mg/kg died within 1-3 days. The LD50 for END treated with brain tissue was 40 mg/kg. Untreated END had previously been reported to have an LD50 of 200 mg/kg and a lethality time of 9 +-3 days. Liver tissue had no effect on toxicity of END. The therapeutic effect of END after incubation with brain or liver tissue was assayed by ip injection of L5222 leukemia cells into rats after incubation of the L5222 cells with END with or without liver or brain homogenates. Incubation with brain homogenates resulted in reductions in the therapeutic effect, as indicated by increased lethality of L5222 cells in rats. Liver tissue did not affect the therapeutic effect of END. Results indicate that incubation with brain homogenates increases the toxicity of END in rats by a factor of 5 and reduces the therapeutic effect. Results suggest that END is not effective in treating brain metastases. END should therefore be used in combination with other agents when metastases of the CNS are present. (8 Refs) (In GER)

41. PREVENTION OF DOXORUBICIN-INDUCED SKIN ULCERS IN THE RAT AND PIG WITH DIMETHYL SULFOXIDE (DMSO).

Desai MH, Teres D
Baystate Medical Center, 759 Chestnut St., Springfield, MA, 01107
Cancer Treat Rep; 66(6):1371-1374 1982

Ten potential agents were tested in the Sprague-Dawley rat, using the method of Rudolph et al, which produces skin ulcers with 0.4 mg of doxorubicin intradermally. One antidote, dimethyl sulfoxide (100%, 0.6 ml for 7 days), prevented ulcer formation not only at the local site but also at the doxorubicin control injection site. Similar ulcers were produced in the Yorkshire pig with 2.0 mg of intradermal doxorubicin injection. These ulcers were prevented at both local and distant control sites with dimethyl sulfoxide given for 7 days. (Author abstract) (9 Refs)

42. EARLY DIAGNOSIS OF BLEOMYCIN PULMONARY TOXICITY USING BRONCHOALVEOLAR LAVAGE IN DOGS.

Fahey PJ, Utell MJ, Mayewski RJ, Wandtke JD, Hyde RW
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Am Rev Respir Dis; 126(1):126-130 1982

Use of the antitumor drug bleomycin sulfate is associated with the development of interstitial pulmonary fibrosis. Presently, diagnosis of this drug-induced pulmonary disease depends on detecting nonspecific changes on chest radiograph. In many instances the fibrosis is extensive and irreversible by the time diagnosis is established with this method. This study was undertaken to determine: (1) if analysis of respiratory cells obtained from bronchoalveolar lavage (BAL) and measurement of static lung compliance (CL) are more sensitive than chest radiograph in detecting early pulmonary injury from bleomycin, and (2) if analysis of BAL fluid provides characteristic findings to aid in differential diagnosis when chest radiographic abnormalities are present. Pulmonary fibrosis was induced in six dogs by twice weekly injections of bleomycin at a dose of 1.25 mg/kg; three untreated animals were used as controls. Every 2 to 4 wk each dog underwent BAL. Analysis of respiratory cells revealed that within the first 4 wk of injection the total number of cells returned significantly increased from 2.4 +-1.1 SD x 10(7) cells to 14.7 +-5.0 x 10(7) cells. Percent polymorphonuclear leukocytes (PMN) increased from 5 +-3% to 15 +-4%, and CL also increased from 0.060 +-0.003 L/cmH2O to 0.074 +-0.014 L/cmH2O during this early period of lung injury. After 8 wk of injection total cell retrieval returned to baseline values, and PMN remained elevated in BAL fluid, whereas CL was significantly decreased. We conclude that analysis of BAL fluid can detect bleomycin-induced pulmonary injury prior to changes in chest radiographs. Increased sensitivity in detecting early pulmonary injury may allow for alteration in drug treatment schedules and result in lower occurrence of pulmonary fibrosis. When chest radiograph demonstrates increased interstitial markings, analysis of BAL fluid reveals an increased percentage of PMN, which aids in differential diagnosis. (Author abstract) (17 Refs)

PHARMACOKINETICS OF ANTITUMOR AGENTS

43. PHARMACOKINETIC ANALYSIS OF ADRIAMYCIN (DOXORUBICIN) AND RELATED FLUORESCENT COMPOUNDS IN EHRLICH TUMOR-BEARING MOUSE PLASMA AND TISSUES.

Shinozawa S, Fukuda T, Araki Y, Oda T
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Acta Med Okayama; 36(2):125-132 1982

Pharmacokinetic analysis of the distribution and concentration of adriamycin (ADM) in mouse plasma and tissues was carried out by differentiating the unmetabolized form from metabolized ones using high-performance liquid chromatography after a single intravenous injection. Marked differences between ADM and total ADM equivalent values (total ADM values) or its metabolized forms were observed in the pharmacokinetic behavior in plasma and tissue distributions. The ratios of tissue per plasma from total ADM and for ADM values in the liver, kidney and heart showed a two-digit magnitude each time they were examined. Twenty four hr later, the ratios for ADM values in the liver, kidney, heart and lung were at high levels; 43.1, 48.1, 57.9 and 45.5 times, respectively. Twenty min after injection the ratios for total ADM values in the spleen, lung and tumors were comparatively small, but 24 hr later, the ratio had increased 36.5, 45.5 and 6.8 times respectively. (Author abstract) (17 Refs)

44. THE DISPOSITION OF 5-IMINODAUNORUBICIN (IMD) IN THE RAT (MEETING ABSTRACT).

Peters JH, Gordon GR, Kashiwase D
Life Sciences Division, SRI International, Menlo Park, CA, 94025
Proc Am Assoc Cancer Res; 23:685 1982

We examined the metabolic disposition of 16 mg ImD/kg, given IV, IP and PO to female Sprague Dawley rats, which were killed at 1, 2, 4, 8 and 24 hr after Rx (therapy). ImD and metabolites in plasma, heart, lung, liver, muscle and brain (stomach contents after PO Rx) were separated by reverse-phase liquid chromatography and quantitated by fluorescence. Plasma decay of ImD was biphasic following IV Rx: alpha-phase half-life equals 1.4 hr; beta-phase half-life equals 11 hr. Only 13-dihydro ImD (ImD-OL) and an unidentified peak (UNK) were found as metabolites. AUC (area under the curve) (ng/ml-hr) of ImD, ImD-OL and UNK for plasma were about the same. Following IP Rx, we found only ImD and ImD-OL in plasma; AUC were nearly identical to those found after IV Rx. After PO Rx only ImD and ImD-OL were detected in plasma; AUC were 1/4 to 1/5 of AUC after IV or IP Rx. The stomach at 1, 2, 4, 8 and 24 hr after PO Rx contained 33.7, 12.1, 11.2, 7.1 and 0.03% of the dose, respectively. Based on AUC (ng/g-hr) after IV Rx, liver levels of ImD, ImD-OL and UNK were 24X, 16X and 8X plasma levels. After IP Rx, liver levels were 92X and 55X plasma levels of ImD and ImD-OL. following PO Rx, liver levels were only 8X and 1.4X plasma levels of ImD and ImD-OL. Small amounts of ImD-ONE and UNK were detected in liver after PO or IP Rx. Also based on AUC, heart levels of ImD and ImD-OL were 42X and 50X those found in plasma after IV Rx. Thus, higher levels of ImD and ImD-OL were found in heart than in liver after IV Rx. After IP Rx, heart levels of these two compounds were slightly less than liver levels; following PO RX, heart levels of ImD and ImD-OL were only 6% and 29% of levels found in liver. (no Refs)

45. CELLULAR PHARMACOKINETICS OF ACLACINOMYCIN A IN CULTURED L1210 CELLS: COMPARISON WITH DAUNORUBICIN AND DOXORUBICIN.

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Cancer Chemother Pharmacol; 8(2):243-249 1982

The cellular pharmacokinetics of aclacinomycin A (ACM), doxorubicin (DOX), and daunorubicin (DNR) in cultured L1210 cells were compared with the aid of cell fractionation techniques and drug determination by high pressure liquid chromatography and fluorometry. The uptake of ACM occurred at a greater speed than that of DNR or DOX, reaching a maximal drug concentration 30 min after incubation. In addition to the parent compound two fluorescent metabolites were separated. Uptake of DNR was biphasic, with an initial rapid phase followed by a slower one, while intracellular DOX levels increased steadily during the assay. ACM was released from cells to the highest extent, about 60% escaping within the first 2 hr. Metabolic inhibitors (iodoacetate or antimycin A) had no effect upon accumulation of ACM, but did affect the release of the drug. Inhibition of incorporation of tritiated thymidine into cellular DNA was more rapid and extensive with ACM than with DNR or DOX. DNR and DOX were associated with DNA and lysosomes while ACM was mainly localized in the nuclei. (26 Refs)

46. PROLONGED RELEASE OF BLEOMYCIN FROM PARENTERAL GELATIN SPHERE-IN-OIL-IN-WATER MULTIPLE EMULSION.

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Chem Pharm Bull (Tokyo); 30(4):1408-1415 1982

A gelatin sphere-in-oil-in-water (S/O/W) multiple emulsion was tested as a vehicle for parenteral administration of bleomycin. Male Wistar rats were injected im with 12 mg bleomycin/kg. Bleomycin was administered in various emulsions and aqueous soln. Sesame oil was used for oil emulsions. Male domestic rabbits were injected with 3 mg bleomycin/kg in the subserosal layer of the appendix. Iv injection aqueous bleomycin in rats produced a max plasma concentration of 70 ug/ml immediately after injection, with a half-life of 30 min. Im injection of aqueous bleomycin produced a max level at 30 min, followed by a rapid decline. S/O/W emulsion produced a significant delay in appearance of bleomycin in the plasma; the max level of 13 ug/ml was reached at 30 min. After oil-in water injection bleomycin appeared rapidly in the plasma, reaching 37 ug/ml at 30 min, and then decreasing rapidly. Sphere-in-oil emulsion and oily suspensions of bleomycin showed levels less than 15 ug/ml throughout the experiment. S/O/W with bleomycin in the external aqueous phase produced a rapid increase in plasma levels, followed by a rapid decline. Bleomycin disappeared from the site of injection more slowly after S/O/W or S/O injections than after aqueous injections. In rabbits S/O and S/O/W produced significant levels of bleomycin in the appendix and lymph nodes at 24 hr, while aqueous injections did not. Evidence indicates that S/O/W emulsion is a potential vehicle for delayed-release parenteral administration of bleomycin, and it is better injectable than S/O emulsion. (17 Refs)

47. CYTOFLUORESCENCE LOCALIZATION OF ADRIAMYCIN IN THE NERVOUS SYSTEM: I. DISTRIBUTION OF THE DRUG IN THE CENTRAL NERVOUS SYSTEM OF NORMAL ADULT MICE AFTER INTRAVENOUS INJECTION.

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Acta Neuropathol (Berl); 57(2/3):121-129 1982

Fluorescence microscopy was used to study the distribution of adriamycin (ADR: 5 or 10 mg/kg) in the CNS of adult male NMRI mice after iv injection. Mice were killed 15 and 30 sec, 1 and 15 min, and 1 and 24 hr after injection. Frozen sections of various parts of the CNS were examined by fluorescence microscopy. The drug was not found in areas of the brain within the blood-brain barrier. Except for the subcommissural organ, ADR was consistently localized in the nuclei of neurons and/or glial cells of the circumventricular organs (postremal area, subfornical organ, median eminence, neurohypophysis) and in cells of the choroid plexus and lamina cribrosa of the optic nerve. While the ADR fluorescence was seen as early as 15 sec, it was most intense after 1 and 15 min. ADR fluorescence disappeared from all regions except the ependyma of the median eminence within 24 hr. The study shows that ADR passes from the blood into the nervous parenchyma in those areas outside the blood-brain barrier. The question is raised as to whether there are any neurotoxicologic effects produced by ADR in these areas which have not yet been detected. (42 Refs)

48. PHARMACOKINETICS OF ALPHA-DIFLUOROMETHYL ORNITHINE IN RAT BRAIN AND IN INTRACRANIAL AND SUBCUTANEOUS 9L TUMORS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:814 1982

The capillary permeability of 14C-DFMO was studied in rat brain and subcutaneous (sc) 9L tumors and the time-dependent uptake of 14C-DFMO was studied in sc and intracerebral (ic) 9L tumors. Since 14C-DFMO is a relatively radiopure and stable compound, tracer studies were sufficient for the pharmacokinetic studies undertaken. 14C-DFMO has a MW equals 237 and a log P equals-2.45. Its brain capillary permeability was 3.9 x 10(-7) cm/sec and is within 5% of that predicted by consideration of its lipophilicity and MW. The permeability x surface area coefficient (PS or Ki) for sc 9L tumor had a median of 0.08 min-1 and 95% confidence limits of .035 to .106 min-1. This was 33 times that for rat brain and somewhat higher than predicted by MW and log P. Time dependent uptake into sc 9L tumors could be accurately predicted by mathematically modeling based on previously determined tumor parameters. To explain why a drug with limited blood-brain barrier penetrability was active against ic 9L tumors we chronically infused 14C-DFMO via intraperitoneally implanted Alza mini pumps for 1 to 4 days and found that the tumor/plasma and brain/plasma ratios were approx equal to 1 at all times within 6 mm of the tumor. These findings are consistent with limited uptake of DFMO by cells, lack of tumor or systemic metabolism, and sustained plasma drug levels and helps to explain the ic tumor activity of DFMO. (3 Refs)

49. COMPARATIVE CEREBROSPINAL FLUID (CSF) PHARMACOKINETICS OF METHOTREXATE (MTX) AND DICHLOROMETHOTREXATE (DCMTX) IN RHESUS MONKEYS (MEETING ABSTRACT).

Zlotecki R, Ensminger W, Knutsen C, Phillips T, Chandler W, Greenberg H, Gyves J
Departments of Medicine, Surgery and Neurology, University of Michigan, Ann Arbor, MI, 48109
Proc Am Assoc Cancer Res; 23:709 1982

The cerebrospinal fluid (CSF) pharmacokinetics of methotrexate (MTX) and dichloromethotrexate (DCMTX) were compared in rhesus monkeys. Ventriculostomy reservoirs were implanted and subcutaneous pumps for continuous infusion were attached to the reservoirs. CSF samples were obtained by lumbar puncture. Drug levels in CSF and plasma were measured by a dihydrofolate reductase inhibition assay. By injecting each of the drugs in combination with Yb-DTPA (diethylenetriamine) (a tracer for bulk flow) it was found that DCMTX was extracted at a much greater rate than MTX (which in turn exceeded Yb-DTPA removal). MTX or DCMTX was infused for 5d at progressive (100%) escalations from 0.034 mg to 1.1 mg/d. Thus, at comparable dose rates, DCMTX achieves lower CSF and systemic levels than MTX suggesting much greater tissue penetration in the central nervous system for DCMTX. No neurological toxicities were detected with either drug. Previous studies have shown that DCMTX is equally potent to MTX in protein free media (such as CSF) but only 1/4th as toxic as MTX systemically (due to serum protein binding). In view of the decreased toxicity and the increased CNS tissue absorption of DCMTX as compared to MTX, DCMTX may be a more efficacious drug in the treatment of meningeal tumors. (no Refs)

50. SYNTHESIS OF POLYGAMMAGLUTAMYL DERIVATIVES OF METHOTREXATE (MTX) IN TUMOR BEARING MICE AND ITS EFFECT ON DRUG PHARMACOKINETICS IN VIVO: CORRELATION OF EXPERIMENTAL DATA WITH COMPUTER SIMULATIONS (MEETING ABSTRACT).

Fry DW, Goldman ID, White JC
Medical College of Virginia, Richmond, VA, 23298
Proc Am Assoc Cancer Res; 23:705 1982

Mice bearing Ehrlich ascites tumor cells were injected subcutaneously with 12 mg/Kg 3H MTX and the pharmacokinetics of total 3H, MTX, and its polyglutamate (MTX-PG) determined in tumor, GI (gastrointestinal) mucosa, plasma and ascitic fluid. No MTX-PG were found in the plasma or ascitic fluid and very little in the GI mucosa. However, MTX-PG well above the dihydrofolate reductase binding capacity accumulated in the tumor. The decline of total 3H and MTX in the GI mucosa paralleled that of the plasma MTX. Similarly, MTX decline in the tumor paralleled that of the ascitic fluid. However, decline of total 3H in the tumor deviated from that of the ascitic due to the presence of intracellular MTX-PG. In the tumor, MTX reached a maximum of 12.0 nmol/g dry wt in 2 hr but fell to 0.36 in 24 hr, whereas maximum MTX-PG was 5.1 but declined to only 3.7. A computer model using existing transport and pharmacokinetic parameters confirmed that the decline of MTX in tumor cells should parallel that in the extracellular compartment since rates of transport for MTX across the cell membrane are much faster than the rate of change in the ascitic fluid. The slower decline of total 3H in these cells supports the contention that MTX-PG exit the tumor more slowly than MTX in vivo. (no Refs)

51. BIOAVAILABILITY AND PHARMACOKINETICS OF ORALLY ADMINISTERED 7-CON-O-METHYLNOGAROL (7-OMEN; NSC 269148) IN THE MOUSE (MEETING ABSTRACT).

Pratt EA, McGovren JP, Adams WJ, Hamilton RD
The Upjohn Company, Kalamazoo, MI, 49001
Proc Am Assoc Cancer Res; 23:672 1982

Previous studies in mice demonstrated equivalent therapeutic activity of ip-and po-administered 7-OMEN against both ip- and iv-inoculated P388 and L1210 leukemias. Optimum doses for po-administered 7-OMEN were about 2-fold higher than for the ip route. In this study, a high performance liquid chromatographic (HPLC) assay was developed and used to measure the plasma concentration-time course of 7-OMEN and metabolites in mice receiving 10 mg/kg doses either iv or po. HPLC assay methods were as follows: 25-500 ul of plasma deproteinized with acetonitrile:methanol was injected directly onto a C8 reverse-phase column. Solvent composition was 0.29 M acetic acid, 0.015 M methanesulfonic acid:acetonitrile (3:2); detection was by fluorescence. The limit of quantitation was about 1.5 ng injected on-column for 7-OMEN and its major metabolite, 7-con-O-methyl-N-demethylnogarol (nor-7-OMEN). The relative areas under the plasma level curves (AUC) from po and iv-treated mice indicated that, although absorption of po-administered 7-OMEN from the GI tract was 80% complete, extensive first-pass hepatic metabolism reduced systemic bioavailability to about 30%. Nor-7-OMEN was prepared synthetically and found to be somewhat less active but about 10-fold more potent at its optimum dose than 7-OMEN in prolonging the life span of mice bearing P388 leukemia and B16 melanoma. Thus, nor-7-OMEN may contribute to the observed antitumor activity of 7-OMEN. (1 Ref)

52. COMPARISON OF THE METABOLISM, KINETICS, AND INHIBITORY ACTION OF ARABINOSYL-2-FLUORADENINE (F-ARA-A) AND ITS 5'-MONOPHOSPHATE (F-ARA-AMP) IN TUMOR BEARING MICE (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:824 1982

The effects of single, equitoxic doses (LD10) of F-ara-A (234 mg/kg) and F-ara-AMP (1485 mg/kg) solutions on P388 cells and host tissues have been compared. F-ara-ATP, the active triphosphate, accumulated in P388 cells of tumor-bearing mice to peak concentrations of 560 uM and 930uM and disappeared with half-lives of 2.9 h and 4.1 h from cells after injection of F-ara-A and F-ara-AMP, respectively. DNA synthesis in P388 cells was inhibited to 1% of controls by 6 h after injection of either drug, but remained below 10% of control values for twice as long (24 h) in cells treated with F-ara-AMP. The life span of tumor-bearing mice injected with F-ara-A one day after tumor inoculation was 110% compared to 48% for mice receiving F-ara-AMP. F-ara-A from both injected compounds passed rapidly from the ascitic fluid into the blood in concentrations proportional to the dose of each. The half-lives of F-ara-A in the plasma were 2.2 h and 3.5 h after ip injection of F-ara-A and F-ara-AMP, respectively. After injection of F-ara-AMP, peak F-ara-ATP concentrations of 34 and 23 nmol/umol DNA purine accumulated in bone marrow (bm) add intestinal mucosa (gi), respectively, and disappeared with identical half-lives of 1.5 h. After injection of F-ara-AMP, maximal inhibition of bm and gi DNA synthesis was 0.4% and 2.1% of control, respectively, whereas F-ara-A injection inhibited bm to 2.8% and gi to 9.4% of controls. Preliminary results suggest that 2-fluoroadenine, which is prominent among the metabolites of both F-ara-A and F-ara-AMP, may be further metabolized to non-arabinosyl nucleotides which may contribute to the toxicity and/or therapeutic activity of these compounds. (no Refs)

53. RAZOXANE PENETRATION INTO THE CEREBROSPINAL FLUID OF RATS.

Greig N, Chang FX, Hellmann K
(c/o Hellman) Cancer Chemotherapy Dept., Imperial Cancer Res. Fund, W2 London, England
Cancer Chemother Pharmacol; 8(2):251-252 1982

Measurements of razoxane (RAZ) concentration in the cerebrospinal fluid (CSF) of rats were made with the aid of a newly developed high pressure liquid chromatographic technique. RAZ was absorbed quickly from the peritoneal cavity, reaching high plasma concentrations within 15 min and a peak concentration of 12.0 ug/ml by 30 min. Levels then declined mono-exponentially. Half-life was about 1.6 hr, with a decay constant of 0.43/hr. Complete elimination occurred by 8 hr CSF RAZ levels rose more slowly and reached a peak of 0.975 ug/ml by 2 hr with a half-life influx of 1.1 hr by which time about 40% of the plasma concentration had been eliminated. The CSF/plasma ratio at the time of peak CSF value was 0.1, and the peak CSF/plasma ratio at 2 hr CSF and 30 min plasma was 0.08. No RAZ was detectable in CSF at 16 hr. These results indicate that RAZ and its analogs are unlikely to be effective in the treatment of malignant disease protected by an intact blood-brain barrier. (6 Refs)

54. THE PHARMACODYNAMIC DISPOSITION OF 1,4-DIHYDROXY-5,8-BIS[[2-[(2 HYDROXYETHYL)AMINO]ETHYL]AMINO]9, 10-ANTHRACENEDIONE BIS-HYDROCHLORIDE (DHAQ) IN RODENTS.

Avramis VI
University of Houston, Houston, TX
Diss Abstr Int [B]; 42(8):3215-B 1982

The binding and preferential accumulation of DHAQ in the chromatin fraction of L1210 leukemic cells in mice has been determined in vivo following 2 mg/kg intraperitoneal (ip) doses. DHAQ and doxorubicin accumulate in a similar pattern in the isolated DNA fraction of L1210 cells in vivo. Peak levels of DHAQ and doxorubicin are found in the DNA fraction at 45 minutes post-treatment. The elimination of DHAQ and doxorubicin from sites of DNA binding is a relatively slow process and may involve the action of exonucleases. A possible mode of action of DHAQ was found to be between 1 and 4 mg/kg after ip dosing. Acute toxicity of DHAQ was evidenced by effects on the cardiovascular and peripheral nervous systems. DHAQ was found to be as active as doxorubicin against L1210 leukemia at equitoxic doses in both BDF1 and DBA/2 mice and was significantly more active in BDF1 mice long-term survivors. Data following intravenous doses of DHAQ 1, 2 and 4 mg/kg to rats were found to fit a three compartment open model. Model independent pharmacokinetic parameters of half-life, clearance and volume of distribution were calculated and the results indicate that DHAQ had a long half-life of elimination (average 93 hr) and shows clearance values of 31.6 to 142 ml/hr with the lower clearance value calculated at the mg/kg dose. The greatest uptake of DHAQ was by L1210, small intestine, liver, kidney, lung, spleen and heart. (no Refs)

55. TUBULIN-DEPENDENT BIOCHEMICAL ASSAY FOR THE ANTINEOPLASTIC AGENT TAXOL AND APPLICATION TO MEASUREMENT OF THE DRUG IN SERUM.

Hamel E, Lin CM, Johns DG
Lab. Medicinal Chemistry and Biology, Developmental Therapeutics Program, NCI, Building 37, Room 6D28, Bethesda, MD, 20205
Cancer Treat Rep; 66(6):1381-1386 1982

A biochemical assay for taxol with sensitivity to 0.1 uM has been developed. Taxol-dependent formation of tubulin polymers occurs at 37 C in 1.0 M glutamate in the absence of GTP. These polymers are cold-stable and hydrolyze GTP at 0 C, whereas tubulin alone will not hydrolyze the nucleotide in the cold. This assay has been used to follow rabbit serum levels of taxol injected iv. Although the drug appears to be almost totally protein-bound, it is nevertheless rapidly cleared from serum. The apparent alpha-phase and beta-phase half-lives after iv bolus administration in one rabbit are 2.7 and 42 mins, respectively. (Author abstract) (8 Refs)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

56. INHIBITION OF EHRLICH ASCITES TUMOR CELL GROWTH BY GRIFFONIA SIMPLICIFOLIA I LECTIN IN VIVO.

Eckhardt AE, Malone BN, Goldstein IJ
(c/o Goldstein) Dept. Biological Chemistry, Univ. Michigan, Ann Arbor, MI, 48109
Cancer Res; 42(8):2977-2979 1982

Griffonia (Bandeiraea) simplicifolia I (G I) seeds contain a family of alpha-D-galactopyranosyl-binding isolectins which strongly agglutinate Ehrlich ascites tumor cells due to the presence of this determinant sugar on their cell surface glycoproteins. Administration of GS I lectin (100 ug/day or 300 ug on alternate days, ip) inhibits the growth of Ehrlich tumor cells in vivo. Mice given injections of only Ehrlich cells lived an average of 36 +-13 (SE) days with no mouse surviving longer than 53 days. Mice given injections of Ehrlich cells and 100 ug GS I lectin daily or 300 ug GS I lectin on alternate days showed 75 and 62% survival, respectively, after 60 days. Lectin-dependent, macrophage-mediated tumor cell lysis may be the mechanism whereby the GS I lectin exerts its cytotoxic effect. (Author abstract) (14 Refs)

57. VITAMIN B6 KILLS HEPATOMA CELLS IN CULTURE.

DiSorbo DM, Litwack G
Oncology Res. Lab., Nassau Hosp., Mineola, NY, 11501
Nutr Cancer; 3(4):216-222 1982

Data are presented which indicate that vitamin B6 (pyridoxine) can retard and eventually kill Fu5-5 rat hepatoma cells in culture. Additional studies indicate that the human kidney cell line 293-31, and a rat glial cell strain, C6, display growth characteristics similar to those of hepatoma cells when cultured in 5 mM pyridoxine-supplemented medium. However, the pyridoxine-supplemented culture medium had little effect on the growth of the human mammary cancer cell line MCF-7. The resistance of the MCF-7 cells to growth inhibition by vitamin B6 suggests that the vitamer pyridoxine must be metabolized to pyridoxal before it can act as a growth inhibitor. These findings suggest the potential use of vitamin B6 as an antineoplastic agent. Possible mechanisms by which vitamin B6 promotes this effect are presented. (Author abstract) (35 Refs)

58. N,N'-DIALKYL-1,2-BIS(HYDROXYPHENYL)ETHYLENEDIAMINES AND N,N'-DIALKYL-4,5-BIS(4-HYDROXYPHENYL)IMIDAZOLIDINES: SYNTHESES AND EVALUATION OF THEIR MAMMARY TUMOR INHIBITING ACTIVITY.

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J Med Chem; 25(7):832-837 1982

Diastereomeric N,N'-dialkyl-1,2-bis(hydroxyphenyl)ethylenediamines (5) were synthesized and tested for their affinity for the estradiol receptor. Only the (+-)-1,2-bis(4-hydroxyphenyl)ethylenediamines with the alkyl groups C3H7 [(+-)-5c, Ka = 1.1 x 10(6)], C4H9 [(+-)-5e, Ka = 3.6 x 10(6)], and C5H11 [(+-)-5h, Ka = 2.2 x 10(6)] showed a marked affinity, which is mainly due to the (+) enantiomers [eg, (+)-5e, Ka = 2.1 x 10(7)]. No enhancement of affinity by cyclization to imidazolidines [eg, (+-)-trans-7a, Ka = 1.2 x 10(7)] was observed. These compounds [eg, (+-)-, (+)-, and (-)-5e], which did not produce any uterine response in the mouse, were able to inhibit weakly the growth of the DMBA-induced mammary carcinoma of the rat. The inhibitory effect of (+-)-5e against MCF-7 cells, which can be overcome by hexestrol, makes a direct antiestrogenic mode of action probable, since general cytotoxic effects and a central action could be ruled out. (Author abstract) (27 Refs)

59. EFFECT OF MOLECULAR STRUCTURES OF N',N'-DISPIROTRIPIPERAZONIUM AND RELATED COMPOUNDS ON THEIR ANTITUMOR AND CYTOTOXIC ACTIVITIES.

Chernov VA, Minakova SM, Ershova IuA, Dvoriantseva GG

S. Ordzhonikidze All-Union Chimicopharmaceutical Inst., Moscow, USSR

Eksp Onkol; 4(3):59-64 1982

Antitumor and cytotoxic activities of various derivatives of prospidin were studied in random-bred albino rats bearing Jensen sarcoma (in vivo experiments) and in cultured sarcoma 45 and chick embryo heart (in vitro experiments). Results of the in vitro experiments showed that prospidin at 1 and 0.1 mg/ml provided 100% and 67%, respectively, inhibition of growth of the sarcoma 45 culture, but did not affect the growth of the chick embryo culture. Substitution of a chlorine atom in the gamma position by an alkylamine or hydroxy group increased the cytostatic effect on the culture of normal tissue and reduced the selective effect on the culture of tumor tissue. Results of the in vivo experiments showed that substituted prospidin derivatives, compared with prospidin, were significantly more toxic for the rats and significantly less active against the Jensen sarcoma. A similar increase in cytotoxicity and decrease in antitumor activity was observed after substitution of two tertiary nitrogen atoms. (12 Refs) (In RUS)

60. SYNTHESIS AND EVALUATION OF THE ANTIMITOTIC ACTIVITY OF NITROSOUREAS DERIVED FROM AMINO ACIDS.

Montero JL, Leydet A, Dewynter G, Seguin A, Favre JM, Imbach JL
Laboratoire de Chimie Therapeutique, Faculte des Sciences d'Abidjan, 04 B. P. 322, Adidjan 04 (RCI), France
Eur J Med Chem Chim Ther; 17(3):257-263 1982

The synthesis of 22 nitrosoureas derived from amino acids and one from a dipeptide is described. Antimitotic activity was tested against the growth of the root of Lepidium sativum and in L1210 leukemia in mice. Relationship of antimitotic activity to constituent amino acids is discussed. (19 Refs) (In FRE)

61. NEW DERIVATIVES OF TRIAZENOIMIDAZOLE.

Pospelova TA, Shafran IuM, Mokrushin VS, Pushkareva ZV, Anoshina GM
Ural Polytechnical Inst., Sverdlovsk, USSR
Khim Farm Zh; 16(5):543-544 1982

Antitumor activity of newly synthesized iminoester and carboxamidines of dimethyltriazenoimidazole was studied in female C57BL mice bearing melanoma B-16. (3',3-Dimethyltriazeno-1)imidazole-4(5)-carboxamidine (compound IV) at 70 mg/kg provided a 60% inhibition of melanoma B-16 growth. Administration of compound IV at 150-220 mg/kg caused death of the animals. (11 Refs) (In RUS)

62. 1.0 METALATION OF 5-ARYL SUBSTITUTED OXAZOLES: TOTAL SYNTHESES OF THE BENZYLISOQUINOLINE ALKALOIDS PAPAVERINE AND ESCHOLAMINE METHIODIDE. 2.0 DIMETHYLALUMINUM METHANESELENOLATE: A NEW REAGENT FOR THE PREPARATION OF ACTIVE ACYL TRANSFER AGENTS. 3.0 TOTAL SYNTHESIS OF THE C-NUCLEOSIDE D,1-SHOWDOMYCIN.

Ames A
University of Pittsburgh, Pittsburgh, PA
Diss Abstr Int [B]; 42(8):3262-B 1982

The total synthesis of the C-nucleosides antitumor-antibiotic showdomycin is described. The synthetic strategy involves a Diels-Alder-retrograde-Dieckmann approach to the molecule. The key intermediate is a bicyclic beta-keto ester, derived from the product of a Diels-Alder reaction between furan and a carboalkoxyketene equivalent, dicarbomethoxyallene. This compound underwent facile functionalization at the alpha-position, and furnished intermediates possessing the beta-ribose configuration after a retrograde-Dieckmannring fragmentation sequence. Further manipulations of several intermediates, besides the ones leading to showdomycin, are also presented. (no Refs)

63. SYNTHESIS OF C5-SUBSTITUTED PYRIMIDINE NUCLEOSIDES AS ANTIVIRAL AGENTS AND CHARACTERIZATION OF NITROXIDE LABELED POLYNUCLEOTIDES AS MOLECULAR PROBES.

Ozinskas AJ
University of Cincinnati, Cincinnati, OH
Diss Abstr Int [B]; 42(8):3238-B 1982

The synthesis of the site-specific spin labeled nucleosides RUGT (ribosyluracil-5-glycosylamidotempo) and DUGT (2'-deoxyribosyluracil-5-glycosylamidotempo), and of the dialkylated nucleosides I-RUGT (N3-labeled RUGT) and I-DUGT (N3-labeled DUGT) was achieved by alkylation of 5-hydroxyuridine (5-OH-U) or of 2'-deoxy-5-hydroxyuridine (5-OH-dU) with 4-(alpha)-iodoacetamido-2,2,6,6 tetramethylpiperidonooxy. The C5-N spin labeled derivatives RUTA (ribosyluracil-5-tempamine) and DUTA (2'-deoxyribosyluracil-5-tempamine) were prepared by condensation of 4-amino-2,2,6,6-tetramethylpiperidonooxy with 5-OH-U or 5-OH-dU. Also prepared were the aniline adducts of 5-OH-U and of 5-OH-dU RUAN (ribosyluracil-5-aniline) and DUAN (2'-deoxyribosyluracil-5-aniline), and the analogous p-toluidine adducts RUTOL (ribosyluracil-5-p-toluidine) and DUTOL (2'-deoxyribosyluracil-5-p-toluidine). Several of the uridine and 2'-deoxyuridine analogs mentioned above were tested for antitumor or antiviral activity. It was established that the RNA analogs, and the DNA analogs DUTA and DUTOL showed little or no activity. DUGT was active against the leukemia P388 cell line. (no Refs)

64. TOXICITY OF MULLERIAN INHIBITING SUBSTANCE TO CELLS DERIVED FROM A HUMAN ENDOMETRIAL TUMOR (MEETING ABSTRACT).

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In Vitro; 18(3,part2):323 1982

A cell line (HEC-1A) derived from a human endometrial tumor is responsive to the presence of Mullerian Inhibiting Substance (MIS) when grown in McCoy's medium in the absence of serum but with the addition of insulin (5 ug/ml), transferrin (5 ug/ml), hydrocortisone (50 nM), EGF (epidermal growth factor) (10 ng/ml) and FGF (fibroblast growth factor) (50 ng/ml). These cells exhibit a 40% reduction in the incorporation of 3H-TDN within 12 h following the addition of MIS to the cultures when compared to similar cultures without MIS. Cells maintained in McCoy's medium with 15% fetal bovine serum show no response to MIS. Other experiments indicate that serum does not inhibit the action of MIS. MIS, isolated for these experiments from neonatal calf Sertoli cells, is a testicular glycoprotein which causes the involution of the Mullerian duct during development of the male fetus. Because the Mullerian duct is the anlage of the uterus and uterine tubes in mammals, it is postulated that cells derived from tumors of Mullerian duct origin must reacquire a sensitivity to the action of MIS by presence of fetal antigens on their cell surface. Additionally, serum must inhibit either the formation or expression of these antigens. (no Refs)

65. ANTITUMOR ACTIVITY IN MICE OF ORALLY ADMINISTERED POLYSACCHARIDE FROM KEFIR GRAIN.

Shiomi M, Sasaki K, Murofushi M, Aibara K

Dept. Biomedical Res. on Foods, Natl. Inst. Health, Kamiosaki, Shinagawa-ku, Tokyo 141, Japan

Jpn J Med Sci Biol; 35(2):75-80 1982

A water-soluble polysaccharide isolated from Kefir grain (KGP) was given po to mice with subcutaneously implanted Ehrlich carcinoma (EC) or sarcoma 180 (S180). The growth of EC and S180 solid tumor was inhibited by 40-59% and 2[illegible]-81%, respectively, by KGP, as compared to the response in untreated mice. KGP also inhibited tumor growth when administered ip. KGP was inactive in vitro against tumor cells. (6 Refs)

66. ANTI-TUMOUR EFFECTS OF THE SESQUITERPENE LACTONE PARTHENIN.

Mew D, Balza F, Towers GH, Levy JG

Dept. Microbiology, Univ. British Columbia, Vancouver, British Columbia V6T1W5, Canada

Planta Med; 45(1):23-27 1982

The in vitro and in vivo antitumor effects of parthenin, a sesquiterpene lactone, were investigated with P815 mastocytoma, L1210 leukemia, and M-1 rhabdomyosarcoma tumor lines in DBA/2 mice. Marked cytotoxic activity was observed in vitro in all cell lines. In vivo studies with ip administration demonstrated increased survival times and cures. (12 Refs)

67. SALTS OF N-ALKYLOXAMIC ACIDS (N-ALKYLAMINOOXOACETIC ACIDS) AS LACTATE DEHYDROGENASE INHIBITORS WITH IN VITRO TOXICITY FOR BURKITT'S LYMPHOMA EB2 CELLS.

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Dept. Chemistry, Univ. Birmingham, P. O. Box 363, Birmingham, B 15, 2 TT, England

IRCS Med Sci [Cancer]; 9(11):1003-1004 1981

Sodium and potassium salts of the N-alkyloxamic acids, and the related series of N,N'-dialkyloxamides and ethyl N-alkyloxamides, were prepared and tested for their effect on oxamate cytotoxicity for tumor and leukemic cells and lactate dehydrogenase (LDH) inhibition, while improving transport and excretion properties. A lack of correlation between the inhibition of LDH and cytotoxicity was observed: the least effective LDH inhibitors were approx 4x more cytotoxic than sodium oxamate. While potassium N-alkyloxamates inhibited LDH in vitro, oxamate's activity as an inhibitor was reduced at least 10-fold. (13 Refs)

68. N-METHYLFORMAMIDE: ANTITUMOUR ACTIVITY AND METABOLISM IN MICE.

Gescher A, Gibson NW, Hickman JA, Langdon SP, Ross D, Atassi G

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Br J Cancer; 45(6):843-850 1982

The antitumor activities of N-methylformamide, N-ethylformamide and formamide against a number of murine tumors in vivo (Sarcoma 180, M5076 ovarian sarcoma and TLX5 lymphoma) have been estimated. In all cases N-methylformamide had significant activity, formamide had marginal or no activity and N-ethylformamide had no significant activity. N-methylformamide and N-ethylformamide were equitoxic to the TLX5 lymphoma in vitro. Formamide was found as a metabolite in the plasma and urine of animals given N-methylformamide and N-ethylformamide, but excretion profiles do not support the hypothesis that formamide is an active antitumor species formed from N-alkylformamides. No appreciable metabolism of N-methylformamide occurred under a variety of conditions with liver preparations in vitro. N-methylformamide, but not N-ethylformamide or formamide, reduced liver soluble non-protein thiols by 59.8% 1 hr after administration of an effective antitumor dose. (Author abstract) (26 Refs)

69. SYNTHESIS AND ANTITUMOR TESTING OF 3-METHENYLTHIOCHROMAN-4-ONE-1,1-DIOXIDE.

Holshouser MH, Loeffler LJ
Dept. Medicinal Chemistry, Sch. Pharmacy, Northeast Louisiana Univ., Monroe, LA, 71209
J Pharm Sci; 71(6):715-717 1982

Treatment of thiochroman-4-one-1,1-dioxide (II) with paraformaldehyde and dimethylamine hydrochloride in isopropyl alcohol at reflux afforded directly in 89% yield the dimeric dihydropyran (IV), corresponding to the dimerization of the target compound 3-methenylthiochroman-4-one-1,1-dioxide (III). Neither the monomer III nor the expected Mannich base, 3-dimethylaminomethylthiochroman-4-one-1,1-dioxide, were isolated under conditions of the reaction. The monomer III could be prepared in 55% yield by sublimation of the dimer IV at 230-250 C; however, redimerization slowly occurred at room temperature. The dimer IV was also prepared by the use of paraformaldehyde and N-methylanilinium trifluoroacetate. The monomer III was found to be marginally active at 10 mg/kg/day versus Ehrlich ascites tumor growth in mice. (Author abstract) (12 Refs)

70. 9-DEAZAADENOSINE, A NEW POTENT ANTITUMOR AGENT (MEETING ABSTRACT).

Chu MY, Landry LB, Klein RS, Lim MI, Bogden AE, Crabtree GW
Division of Biology, Roger Williams General Hospital, Brown University, Providence, RI, 02908
Proc Am Assoc Cancer Res; 23:867 1982

The growth inhibition of 9-deazaadenosine (9-DAA), against 9 human solid human tumor lines (HRT-18; mesothelioma, VAMT-1; EP Breast; HCT-8, melanoma, Tang; MW Breast; pancreatic carcinoma, DAN; lung carcinoma LX-1 and ovarian carcinoma) was evaluated. ID50 values ranged from 1-8.5 x 10-8M. Studies with pancreatic carcinoma, DAN, in ATS-mice showed that 9-DAA (0.5 mg/kg/day for 3 days) reduced tumor weight to 16% of controls. Some weight losses and/or deaths were noted. Host toxicity was reduced when p-nitrobenzyl-6-thioinosine (NBMPR) a nucleoside transport inhibitor, was used in combination with 9-DAA. In vitro studies with pancreatic carcinoma, DAN and ovarian carcinoma cells showed that 9-DAA (10-5M for 2 hr) caused 34 and 68% inhibition of [3H]-uridine incorporation into RNA and DNA, respectively, and inhibited [3H]-thymidine incorporation into DNA by 80%. In these studies, peak which appeared in the triphosphate region of nucleotide profiles (determined by anion-exchange high pressure liquid chromatography) was tentatively identified as 9-deazaATP. These studies demonstrate that (1) 9-DAA is a potent growth inhibitor of 9 types of human solid tumor cell lines in vitro and of pancreatic carcinoma, DAN in vivo, (2) host toxicity to 9-DAA can be reduced by pretreatment with NBMPR, (3) 9-DAA can be incorporated into the nucleotide pools of treated cells and (4) 9-DAA may exert its effects, in part, by inhibiting the synthesis of RNA and DNA. (no Refs)

71. EXPERIMENTAL ANTITUMOR ACTIVITY AND TOXICITY OF A NEW ANTIBIOTIC: BBM 928A (MEETING ABSTRACT).

Rose WC, Schurig JE, Huftalen JB, Bradner WT
Bristol Laboratories, Syracuse, NY, 13201
Proc Am Assoc Cancer Res; 23:790 1982

The experimental antitumor activity and toxicity of a new antibiotic, BBM 92A (Syn: Luzopeptin A), was evaluated in tumor-bearing and normal mice. When administered as a suspension in saline, the compound demonstrated good activity (T/C values greater than 150%) against ip B16 melanoma (B16) and ip P388 leukemia (P388), and weak activity (T/C values of 125-150%) versus iv P388, ip L1210 leukemia (L1210), Lewis lung (LL) and Madison 109 lung (M109) carcinomas. It was inactive against ip Colon 26 (C26) and sc M109 carcinomas. In comparison to echinomycin, which it resembles in structure, BBM 928A performed very similarly against various murine tumors. For example, against ip B16, BBM 928A displayed some superiority but it was comparable against ip L1210, P388, LL and C26, and slightly inferior in the ip M109 model. A soluble formulation of BBM 928A was found to be equivalent in activity to the suspension against ip P388 and B16. In toxicity studies, the soluble formulation, which had an LD50 of 0.1 mg/kg, did not cause leukopenia, nephrotoxicity or hepatoxicity as indicated by the lack of an effect upon total white blood cell counts, blood urea nitrogen levels and serum glutamic pyruvic transaminase levels, respectively. Although there was no leukopenia, there was a dose-related neutrophilia and lymphopenia. Because of its antitumor activity, novel structure, good potency, high binding affinity to DNA, and apparent lack of certain organ toxicities, further development of BBM 928A or its analogs is being considered. (no Refs)

72. EVALUATION OF BENZALDEHYDE(BA) AS A CHEMOTHERAPEUTIC AGENT (MEETING ABSTRACT).

Taetle R, Howell S, Koessler A
Departments of Medicine and Pathology, University of California, San Diego, CA, 92103
Proc Am Assoc Cancer Res; 23:784 1982

Benzaldehyde is a naturally occurring compound extracted from figs and released during bacterial degradation of amygdalin (Laetrile) that has been reported to have anti-tumor activity. We have tested BA as benziladine glucose against a variety of human tumors in vitro and against human tumor xenografts. BA was tested over a concentration range of 0.1 to 100 ug/ml against human marrow granulocyte/macrophage progenitors (CFU-GM) and showed dose-dependent inhibition at 10-100 ug/ml. HL60 promyelocytic leukemia colonies were significantly more sensitive than CFU-GM at concentrations of 50 and 100 ug/ml. However, HL60 cells were not inhibited by BA in liquid culture, and KG-1 myelocytic leukemia colonies were resistant to the drug. B-CLL colonies from 2 pts were also resistant to BA. When administered to athymic mice bearing human tumor xenografts at doses of 25 or 50 mg/kg, BA had no effect on tumor growth or non-tumor weight of a colon carcinoma (T380) or an epidermoid carcinoma (T222). Colonies of T222 cells and an astrocytoma xenograft grown in agar were resistant to BA. Histologic sections of T380 and T222 tumors and cytospins of HL60 cells exposed to BA showed no evidence of increased differentiation. Human tumor colony forming units grown from biopsies of 10 pts (7 ovarian, 1 breast, and 1 epidermoid carcinoma and 1 medullablastoma) were tested against BA. Only 1 ovarian carcinoma showed greater than 70% inhibition at 100 ug/ml. (no Refs)

73. INHIBITION OF IN VITRO GROWTH OF PANCREATIC ADENOCARCINOMA CELL LINES BY 7-O-METHYLNOGAROL (7-OMEN) (MEETING ABSTRACT).

Chang BK
Medical College of Georgia, Augusta, GA, 30910
Proc Am Assoc Cancer Res; 23:681 1982

Because of the need for improvement in the therapy of pancreatic adenocarcinoma, screening of a number of chemotherapeutic agents was undertaken against a panel of pancreatic cancer cell lines: 2 of human origin, PANC-1 and COLO-357; and 2 of hamster origin, WD PaCa (well-differentiated pancreatic ductal adenocarcinoma; a solid tumor model, adapted to tissue culture prior to use in these experiments), and PD PaCa (poorly-differentiated PaCa; an ascitic model, which grows readily as a single cell suspension in culture). For dose-survival determinations, cells were harvested in early stationary phase and incubated at 37 C, 3% CO2, for 1 hour with drug concentrations of 0, 0.01, 0.1, 1.0, 10, 100 ug/ml. Cells were washed free of drug and resuspended in complete media with 15% fetal bovine serum, glutamine and Pen/Strep. PD PaCa cells were assayed by colony formation in 0.9% methylcellulose media after 7-10 days incubation. The adherent cell lines were assayed 24 hours after drug exposure by microcytotoxicity in Terasaki plates. Drug sensitivity was defined as an ID50 of less than 1 ug/ml for the colony formation assay and less than 10 ug/ml for the microcytotoxicity assay. 7-OMEN was the only agent to which all of the cell lines showed sensitivity. PD PaCa responded to 4 additional drugs (adriamycin, actinomycin D, cis-platinum and NSC 301739). (no Refs)

74. EVALUATION OF MARCELLOMYCIN USING AN IN VIVO MODEL FOR STUDYING DRUG-INDUCED LEUKEMIA CELL DIFFERENTIATION (MEETING ABSTRACT).

Schwartz EL, Brown BJ, Nierenburg M, Marsh JC, Sartorelli AC
Departments of Pharmacology and Medicine, Yale University School of Medicine, New Haven, CT, 06510

Proc Am Assoc Cancer Res; 23:678 1982

An in vivo clonal assay was developed to examine the capacity of chemical and biological agents to induce the differentiation of HL-60 human acute promyelocytic leukemia cells. This technique was used to study the anthracycline marcellomycin. HL-60 cells in 0.3% agar were placed in diffusion chambers and implanted in the peritoneal cavity of mice. The animals then received a single iv dose of marcellomycin. After 24 hrs, the chambers were transferred to new animals. After 8 days, chambers were removed and cells stained with nitro blue tetrazolium and Wright's stain. The cell generation time in vivo was equal to that occurring in suspension culture in vitro; cloning efficiency in vivo was 47%. Marcellomycin produced a dose dependent decrease in cloning efficiency, with a 40% reduction at 10 mg/kg. The drug also enhanced the commitment of HL-60 cells to differentiate, producing both purely differentiated colonies and mixed differentiated-undifferentiated colonies. The rate of commitment was approximately 20% at 10 mg/kg marcellomycin, compared to 2% in non-drug treated animals. The average size of differentiated colonies was 16 cells, and colony size was not affected by drug treatment. No differentiated colonies greater than 32 cells were observed, implying that HL-60 cells are capable of a maximum of 5 divisions after commitment to maturation. This technique permits an estimate of the rates of cell kill and commitment to differentiation, while allowing for consideration of pharmacokinetic characteristics of the drug. (no Refs)

STUDIES OF ANTIMETASTATIC AGENTS

75. ROLE OF NK CELLS IN THE CONTROL OF METASTATIC SPREAD AND GROWTH OF TUMOR CELLS IN MICE.

Gorelik E, Wiltrout RH, Okamura K, Kabu S, Herberman RB
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Int J Cancer; 30(1):107-112 1982

The ability of BALB/c nude and C57BL/6 mice to eliminate tumor cells from the blood stream was severely impaired after a single inoculation of 0.2 ml of anti-asialo BMI (asGMI) serum, diluted 1:40 to 1:320. The number of iv-inoculated YAC-I cells surviving in the lungs of BALB/c nude mice pretreated with anti-asGMI serum was 28x higher than in the control nude mice. The increase in the initial survival of tumor cells that was induced by pre-treatment with anti-asGMI resulted in a substantial increase in the number of artificial lung metastases that developed. In C57BL/6 +/+ mice treated with anti-asGMI and in C57BL/6 beige mice, iv inoculation of B16 melanoma cells induced 10x more metastatic foci in the lungs than in the control C57BL/6 +/+ mice. In contrast, in nude mice which possess higher levels of NK reactivity, metastatic growth was suppressed seven-fold in comparison with intact C57BL/6 +/+ mice. Data indicate that B16 melanoma cells are able to grow in the liver, but their growth is ordinarily prevented by NK cells. The antimetastatic defense of C57BL/6 mice treated by anti-asGMI could be restored by transplantation of 40 x 10(6) normal spleen cells. This antimetastatic effect of transplanted spleen cells was mediated by asGMI-bearing cells since after in vitro pretreatment of normal spleen cells with anti-asGMI and complement, they lost their ability to inhibit the development of artificial metastases in the lungs of C57BL/6 mice. Suppression of NK reactivity by multiple injections of anti-asGMI in C57BL/6 mice inoculated intrafootpad with B16 melanoma or 3LL tumor cells, did not influence the growth of local tumors, but dramatically accelerated the development of spontaneous pulmonary metastases. These data demonstrate that NK cells may play an important role in resistance to the dissemination of tumor cells, and therefore contribute to the control of metastasis formation in mice. (21 Refs)

76. EXPERIMENTAL HEMATOGENIC METASTASES OF MALIGNANT SCHWANNOMA IN THE RAT.

Mandybur TI, Brunner GD
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Acta Neuropathol (Berl); 57(2/3):151-157 1982

The development, growth patterns and morphology of metastatic schwannomas was studied in adult Lewis rats injected iv with malignant cells from an ethylnitrosourea-induced malignant schwannoma. Groups of 10 rats received doses of 0.1, 0.5, 1.0, 5.0, 10, and 100 x 10(5) cells, respectively. Mortality before day 34 was one each in groups with the lowest doses, and 4, 5 and 10 in those with the highest doses, respectively. Lung metastases developed in all animals in all treated groups, but they varied as to location, form, size and frequency that partly depended upon the cell dose. Lung metastases were in the form of microscopic and macroscopic peripheral subpleural tumors, central peribronchial and perivascular tumors, parenchymal tumors, diffuse intraalveolar infiltrates and intravascular tumor emboli. The variety of metastatic tumors was greater in groups that received the higher cell doses. Metastatic tumors of the pericardium were also found in 36 rats. In 13 rats metastatic tumors occurred in kidney, heart, ovary, adrenal gland, intestine, or skeletal muscles. While more organs became involved as cell dose increased, no tumors developed in the brain. (8 Refs)

INTERFERON AND OTHER ANTIVIRALS

77. MICROINJECTION OF INTERFERON AND 2',5'-OLIGOADENYLATE INTO MOUSE L CELLS AND THEIR EFFECTS ON VIRUS GROWTH.

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J Biochem (Tokyo); 91(6):2021-2028 1982

By means of a new type of microinjection apparatus, which has a micropipette located in a hole through the optical axis of the condenser lens, we injected interferon (IFN) or 2',5'-oligoadenylate (2-5A) into mouse L cells, and observed their antiviral effects on the multiplication of vesicular stomatitis virus (VSV). After injection, cells were infected with VSV, and labeled with [3H]uridine in the presence of actinomycin D. The proportion of cells infected with VSV which carried radioactive virus-RNA was determined by autoradiography. IFN introduced directly into L cells had no effect on the virus growth. This result supports the idea the IFN molecules exert their effect from outside the cell membrane without penetrating into the cytoplasm. 2-5A, on the other hand, was able to inhibit the growth of VSV effectively when injected into L cells. The antiviral effect was dependent on the dose of 2-5A injected, and moreover the effect was transient, since it disappeared completely after 24-h incubation. (Author abstract) (28 Refs)

78. INTERFERON INDUCTION AND THERAPY OF BRAIN TUMORS IN RATS BY POLY(ICLC).

Machida H, Takezawa J, Kuninaka A, Yoshino H, Nakamura O, Takakura K

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Microbiol Immunol; 26(4):353-358 1982

Comparative interferon-inducing and antitumor activities of poly(ICLC) and poly(I)poly(C) were studied in male SD rats and in female Wistar rats with intracerebrally transplanted glial tumors. The preparation containing 1 mg of poly(I)poly(C) and 0.5 mg of poly-L-lysine (poly(ICLC)-B) and the preparation containing 1 mg of poly(I)poly(C) and 0.75 mg of poly-L-lysine (poly(ICLC)-A) had the higher melting temperature and greater resistance to human RNase than the parental poly(I)poly(C). The levels of plasma interferon after injection of poly(ICLC)-A was lower than those after injection of poly(ICLC)-B or poly(I)poly(C). Poly(ICLC)-B induced more prolonged elevation of plasma interferon titers than poly(I)poly(C). Treatment with poly(ICLC) prevented the loss of body wt and increased the life-span of rats bearing glial tumors. The antitumor activity of poly(ICLC) was correlated with persistence of the high level of plasma interferon. Treatment with poly(ICLC)-B (0.5 mg/kg, 3x/wk) was as effective as the treatment with aminochloroethyl nitrosourea (5 mg/kg). (14 Refs)

79. INTERFERON ENHANCEMENT OF THE INVASIVE CAPACITY OF EWING SARCOMA CELLS IN VITRO.

Siegal GP, Thorgeirsson UP, Russo RG, Wallace DM, Liotta LA, Berger SL
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Proc Natl Acad Sci USA; 79(13):4064-4068 1982

The ability of interferons to reduce cell proliferation in vitro and in vivo is a well-studied phenomenon. To extend such observations, the effect of interferons on the invasiveness in vitro of human malignant cells derived from a Ewing sarcoma was evaluated. Two related parameters were examined: (i) production of Type IV (basement membrane) collagenase and (ii) penetration of human amnion basement membrane and collagenous stroma. After 6 days of treatment with crude fibroblast interferon, leukocyte interferon, or lymphoblastoid interferon at 100 units/ml in serum-free medium, Type IV collagenase levels increased two- to four-fold per cell relative to those of untreated controls. With homogeneous fibroblast and lymphoblastoid interferons, a two-fold elevation in Type IV collagenase was detected after 2 days, with further increases, occasionally dramatic, occurring on the 4th and 6th day of treatment. The ability of Ewing sarcoma cells to invade human amnion connective tissue was measured after 6 days of treatment with various interferons. Relative to the behavior of untreated controls, crude leukocyte interferon, homogeneous lymphoblastoid interferon, and homogeneous fibroblast interferon at 100 units/ml augmented invasiveness 3-, 17-and 22-fold, respectively, when cells were allowed 4 days in which to traverse the amnion. When untreated cells were exposed simultaneously to the amnion and to homogeneous lymphoblastoid or fibroblast interferon, a four- to five-fold increase in invasiveness above control levels was observed in 2 days. These data emphasize the complexity of interferon-induced phenomena. In any overview, the effects of interferon on both the tumor cell and the host must be considered. (Author abstract) (27 Refs)

80. MECHANISM OF STIMULATION BY HUMAN INTERFERON OF PROSTAGLANDIN SYNTHESIS IN HUMAN CELL LINES.

Fuse A, Mahmud I, Kuwata T
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
Cancer Res; 42(8):3209-3214 1982

Human interferon beta (IFN-beta) stimulated the synthesis of prostaglandin E (PGE) and prostaglandin F2alpha in IFN-sensitive RSa and GM258 cell lines, but not in IFN-resistant HEC-1 cells. IFN-beta at a concentration of 1,000 units/ml elicited two- to three-fold increases in PGE production in these cell lines. In the presence of exogenous arachidonic acid (1 ug/ml), IFN-pretreated cells produced five-fold more PGE compared to the cell cultures in the absence of arachidonic acid. Prednisolone, an inhibitor of phospholipase A2, at a concentration of 2 ug/ml inhibited the enhanced synthesis of PGE by IFN-pretreated cells. Indomethacin (4 ug/ml), a potent fatty acid cyclooxygenase inhibitor, also inhibited the increased synthesis of PGE. IFN stimulated the release of [14C]arachidonic acid from phospholipids but did not stimulate the activity of fatty acid cyclooxygenase. These data suggest that IFN stimulates prostaglandin synthesis by promoting the release of arachidonic acid from phospholipids. Since cycloheximide and actinomycin D inhibited the stimulation of PGE synthesis, the stimulation of prostaglandin synthesis by IFN seemed to be due to de novo enzyme synthesis, which catalyzes the release of fatty acid. Addition of exogenous PGE suppressed the growth of RSa and GM258 cells. Prednisolone and indomethacin partially inhibited anti-cell growth activity of IFN, suggesting a possibility that IFN-inhibited cell growth was partly mediated by prostaglandins. (Author abstract) (55 Refs)

81. DIFFERENTIAL EFFECTS OF HYDROXYUREA ON THE SURVIVAL OF UV- AND MNNG-TREATED ADENOVIRUS 5.

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Mutat Res; 94(2):257-262 1982

Effects of hydroxyurea (HU) on the survival of both UV- and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) treated adenovirus 5 when used to infect either human cell strains XP12BE, CRL1220, XP4BE, and KD were studied and observed that HU decreased in all cases studied the survival of UV-irradiated adenoviruses. A 24-hr 10-milliM (mM) HU postinfection treatment of XP12BE fibroblasts caused apparent increase in sensitivity of UV-irradiated adenovirus 5. The magnitude of inhibition of viral recovery by HU, however, was less than that observed when infecting normal fibroblasts. In the presence of HU, the lethality of a given dose was increased by a factor of 2.1 in normal, cells, and by 1.29 using the XP12BE strain. In ancillary experiments, 10 mM HU present with KD cells only during the 24 hr prior to infection caused no enhancement of viral inactivation. HU (10 mM) applied to CRL1187 or KD normal fibroblasts (Mer+) infected with MNNG-treated adenoviruses caused no change in viral survival indicating that HU does not interfere greatly with the Mer repair pathway. However, HU treatment did increase the survival of MNNG-treated viruses when infecting the A1336 and A172 Mer- strains, the lethality of a given dose being increased by 1.52 +-0.10. The result showed that viral recovery occuring independently of the Mer system is somewhat susceptible to blockage by the HU treatment. (26 Refs)

82. INHIBITORY EFFECT OF E-5-(2-BROMOVINYL)-1-BETA-D-ARABINOFURANOSYLURACIL ON HERPES SIMPLEX VIRUS REPLICATION AND DNA SYNTHESIS.

Descamps J, Sehgal RK, De Clercq E, Allaudeen HS
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J Virol; 43(1):332-336 1982

The effect of E-5-(2-bromovinyl)-1-beta-D-arabinofuranosyluracil (BVaraU) on herpes simplex virus (HSV) replication was examined and compared with that of E-5-(2-bromovinyl)-2'-deoxyuridine (BVdUrd). The 50% inhibitory dose against HSV type 1 (HSV-1) was 0.1 ug/ml compared with 0.008 ug/ml for BVdUrd; the antimetabolic 50% inhibitory dose of BVaraU ranged from 20 to 95 ug/ml. The addition of 50 ug of BVaraU per ml to HSV-1-infected Vero cells decreased the synthesis of viral and cellular DNA by 37 and 28%, respectively. The 5'-triphosphate (BVaraUTP) competed with dTTP in DNA synthesis by the herpes-viral and cellular DNA polymerases; the apparent Ki values of HSV-1 DNA polymerase, DNA polymerase alpha, and DNA polymerase beta were 0.14, 0.32, and 5 uM, respectively. Thus, BVaraU was a less effective antiherpesvirus agent than BVdUrd; unlike BVdUrd, it did not appear to be internally incorporated into replicating DNA in virus-infected cells. (Author abstract) (13 Refs)

83. INHIBITION OF TRANSLATION OF SATELLITE TOBACCO NECROSIS VIRUS (STNV) RNA MODIFIED BY (+/-)-7BETA,8ALPHA-DIHYDROXY-9ALPHA,10ALPHA-EPOXY 7,8,9. 10-TETRAHYDROBENZO[A]PYRENE (BPDE) IN A WHEAT GERM CELL-FREE SYSTEM (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:250 1982

A previous study from this laboratory showed that BPDE modification of rabbit globin mRNA results in inhibition of translational initiation. It was of interest to explore the possibility that modification of the 5' cap structure was responsible for this inhibition. Therefore, we reacted the naturally non-capped mRNA from STNV with BPDE and translated it in a wheat germ cell-free system. The extent of modification was 1.3 and 2.9 BPDE residues/molecule. High performance liquid chromatography of the modified nucleosides from enzymatically hydrolyzed STNV RNA reveals that more than 90% of the nucleoside adducts were substituted at the exocyclic amino group of guanosine. The translational ability of the modified STNV, measured by incorporation of [14C] amino acids into acid-precipitable polypeptides is inhibited by about 60%. Polyacrylamide gel electrophoretic analyses of the translation products indicate that only full-length coat proteins are synthesized but with the carcinogen-modified STNV the amount is reduced. On the other hand, 80S initiation complex formation was not inhibited as measured by binding of the BPDE-modified STNV to ribosomes and followed by glycerol gradient centrifugation. Under these conditions, aurintricarboxylic acid completely inhibits 80S initiation complex formation in the presence of both modified and native STNV. (no Refs)

OTHER RELATED STUDIES

84. INTERACTION OF METHOTREXATE POLY(L-LYSINE) WITH TRANSFORMED HEPATIC CELLS IN CULTURE.

Galivan J, Balinska M, Whiteley JM
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Arch Biochem Biophys; 216(2):544-550 1982

Role of poly(L-lysine) as a carrier for methotrexate (MTX) was studied in H35 hepatoma cells and their transport-resistant counterparts, H35R0.3 cells. H35 andH35R0.3 cells were equally susceptible to MTX poly(L-lysine), but an 86-fold difference in the sensitivity to MTX was observed, which was reflected in the reduced uptake of MTX by the resistant subline. Both cell types accumulated much more MTX linked to poly(L-lysine) than MTX alone. MTX poly(D-lysine) was accumulated by both cell types to the same extent as the L-conjugate. MTX poly(L-lysine) completely inhibited cell growth at 200 nanoM, whereas a comparable concentration of poly(L-lysine) alone caused only a modest (less than 10%) inhibition of cell growth. MTX poly(L-lysine) exhibited extensive hydrolysis in H35 and H35R0.3 cells. Uptake of MTX by H35 cells was severely depressed in the presence of folinic acid. In contrast, inclusion of folinic acid during [3H]MTX poly(L-lysine) uptake had no effect on cellular accumulation of the unbound MTX pool demonstrating that cellular entry of the complex proceeds the liberation of MTX. Results demonstrated that MTX poly(L-lysine) enters the cells as an intact complex independent of the MTX and reduced folate coenzyme transport system. MTX poly(L-lysine) is then hydrolyzed yielding MTX by a lysosomal mechanism. The liberated MTX or its polyglutamate forms are then free to bind to the target site, dihydrofolate reductase, resulting in a blockage of folate coenzyme function. (21 Refs)

85. LEUCOVORIN REVERSAL STUDIES WITH TMQ AND A TRIAZINE ANTIFOL IN COMPARISON WITH METHOTREXATE (MEETING ABSTRACT).

Broome MG, Johnson RK, Evans SF, Wodinsky I
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Proc Am Assoc Cancer Res; 23:699 1982

We previously reported that, unlike methotrexate (MTX), 5-methyl-6-[[(3,4,5-trimethoxyphenyl)amino]methyl]-2,4 quinazolinediamine (NSC 249008, TMQ) and 3-chloro-4-[4-[2-chloro-4-(4,6-diamino-2,2-dimethyl-sym triazin-1(2H)-yl)-phen yl]butyl]benzenesulfonyl fluoride (NSC 127755, triazine antifol) inhibit uridine and thymidine incorporation by P388 cells at 100 uM. The present studies were done to determine whether these effects contribute to the cytotoxicity and/or antitumor activity of TMQ and triazine antifol. Leucovorin at 100 uM partially reversed the inhibition of deoxyuridine incorporation in P388 cells by 10 uM MTX, TMQ, or triazine antifol. However, leucovorin had no influence on the inhibition of uridine or thymidine incorporation by TMQ or triazine antifol suggesting that these effects are not due to inhibition of dihydrofolate reductase (DHFR). Inhibition of proliferation of P388 cells in culture by continuous exposure to MTX and triazine antifol was readily reversed by leucovorin, whereas the inhibitory effect of TMQ was much less reversible. However, the cytotoxic effects of all three antifols to P388 cells as measured by cloning efficiency in soft agar were reversed by leucovorin. Thus, the cytotoxic effects of all three antifols would appear to be a function of inhibition of DHFR, whereas other properties of TMQ appear to play a role in inhibition of proliferation of P388 cells in vitro. (no Refs)

86. POLYGLUTAMATE (PG) METABOLITES PROLONG METHOTREXATE (MTX) ACTION IN BREAST CANCER CELLS (MEETING ABSTRACT).

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Clinical Pharmacology Branch, National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:704 1982

To determine the importance of MTX PG's in MTX action, we compared their synthesis, retention, and effects in 3 human breast cancer cell lines. PG's up to 5 glutamates in length were analyzed by HPLC (high pressure liquid chromatography). Enzyme-bound was separated from free drug by DEAE (diethylaminoethanol) Sephacel chromatography. After 24-hr incubations with 2 M 3H-MTX and 10 uM thymidine and inosine to prevent cytotoxicity, PG's accounted for 56% of intercellular drug in MCF-7 cells and 93% of drug in ZR-75-1 cells, but less than 5% drug in MDA-231 cells. These differences could not be explained by inability to transport MTX, since all 3 cell lines contained 3-8 nmoles/g free drug, not no PG's, after 1-hr incubations. When MCF-7 and ZR-75-1 cells, pre-incubated for 24 hrs with 2 uM MTX and rescue medium, were resuspended in drug-free medium, they rapidly lost free MTX, but retained higher PG's in excess of dihydrofolate reductase (DHFR). PG3,4 and 5 accounted for 79% of retained drug in MCF-7 cells, and PG5 alone for 58% in ZR-75-1. After 24-hr incubations in drug-free medium, dU incorporation into DNA remained inhibited to 30-35% control in MCF-7 and ZR-75-1 cells, and there was a 30% decline in cell numbers. In contrast, the MDA-231 cells which did not contain PG's after culture in 2 uM MTX, did not retain MTX in excess of DHFR when resuspended in drug-free medium, recovered ability to incorporate dU (deoxyuridine) by 6 hr, and had no decrease in cell numbers in absence of MTX. When cultured in 10 uM MTX, MDA-231 cells formed PG's in excess of DHFR, and showed prolonged inhibition of dU incorporation in drug-free medium. (no Refs)

87. DEFECTIVE REMOVAL OF DNA CROSS-LINKS IN A REPAIR-DEFICIENT MUTANT OF CHINESE HAMSTER CELLS.

Meyn RE, Jenkins SF, Thompson LH
Dept. Physics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Res; 42(8):3106-3110 1982

To further understand the relationships between DNA damage, DNA repair, and cellular end points such as survival and mutation, the repair capacity of a DNA repair-deficient mutant (strain UV-20) of Chinese hamster ovary cells was characterized in response to DNA cross-linking agents. This mutant, previously shown to be hypersensitive to killing by both ultraviolet light and the cross-linking agent mitomycin C, was also found to be extremely sensitive to cis-diamminedichloroplatinum, another DNA cross-linking agent. The efficiency of DNA cross-link removal after treatment with mitomycin C or cis-diamminedichloroplatinum was measured using the technique of alkaline elution and compared in wild-type Chinese hamster ovary cells and strain UV-20. Wild-type cells removed 80 or 95% of the cross-links within 24 hr after treatment with cis-diamminedichloroplatinum or mitomycin C, respectively. In contrast, UV-20 cells, which were equally as susceptible to cross-link damage as were wild-type cells, removed only a small proportion of the cross-links made by either agent. These results emphasize the importance of DNA repair processes in modulating the cytotoxic effects of chemicals that produce DNA cross-link damage and suggest that cross-link repair in chinese hamster ovary cells is controlled by pathway that also repairs damage from ultraviolet radiation. (Author abstract) (26 Refs)

88. HYPERSENSITIVITY OF ATAXIA TELANGIECTASIA SKIN FIBROBLASTS TO DNA ALKYLATING AGENTS.

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Mutat Res; 94(2):369-382 1982

Three ataxia telangiectasia (AT) skin fibroblasts cells strains, AT4BI, AT5BI, and AT2BE (CRL 1343) were studied for survival following treatment with methyl methanesulfonate (MMS), ethyl methanesulfonate (EMS), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), and 4-nitroquinoline-1-oxide (4NQO) and results were compared to those obtained from three normal human fibroblast cell strains. None of the AT fibroblast strains were significantly more sensitive to MNNG treatment than the av normal survival. Similarly, no significant difference was observed in D10 values among the AT fibroblast strains and the normal av D10 value. Strain AT5BI appeared to be moderately sensitive to MMS treatment compared to the normal av survival. Comparison of the D0 value for strain AT5BI, 0.29 milliM (mM) vs the normal av of 0.38 +-0.03 mM indicated a significant difference in the slope of the survival curve between strain AT5BI and the normal av survival curve. Strain AT4BI was hypersensitive to MMS treatment only when D0S were compared. All three fibroblast strains were significantly more sensitive to treatment with EMS than the normal controls. AT4BI, AT5BI, and AT2BE had D10S of 16, 13, and 15 mM, respectively, vs the normal human fibroblast av D10 value of 28 mM. AT4BI and AT2BE were abnormally sensitive to treatment with 4NQO as compared to the survival of the normal human fibroblast strains. (61 Refs)

89. DNA STRAND BREAKS AND CYTOTOXICITY PRODUCED IN L1210 CELLS BY 3 CLASSES OF INTERCALATING AGENTS (MEETING ABSTRACT).

Kerrigan D, Zwelling L, Michaels S, Pommier Y, Kohn K
National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:769 1982

Treatment of mammalian cells with several types of intercalating agents leads to the formation of protein-associated DNA strand breaks, possibly by an enzymatic mechanism. Both single-strand (SSB) and double-strand breaks (DSB), but at different ratios, are produced by various intercalators. The current work asks whether intercalator-induced cytotoxicity in L1210 cells is dependent upon the formation of either single-strand or double-strand breaks. If this is true, then doses of different intercalating agents producing equal break frequencies should produce equal cytotoxicity. The following representatives of 3 chemical classes of intercalators were tested: 4'-(9-acridinylamino)-methanesulfon-m-anisidide (m-AMSA), 2-methyl-9-hydroxyellipticinium (OHE), and 5-iminodaunorubicin (5ID). These drugs were chosen because the DNA breaks which they produce are reversible, thus permitting a meaningful quantitative comparison between DNA breaks and loss of colony-forming ability. Single- and double-strand breaks were measured by means of filter elution at pH 12.1 and 9.6 respectively, utilizing proteinase-K. We find no uniform relationship between the frequency of SSB's or DSB's and cell killing produced by different intercalating agents. The results are consistent with the view that protein-associated strand breaks may have a functional rather than a cytotoxic significance. (no Refs)

90. EFFECT OF HIGH-DOSE OESTROGEN ADMINISTRATION ON THE GROWTH AND PROLACTIN RECEPTOR CONTENT OF N-NITROSOMETHYLUREA-INDUCED MAMMARY TUMOURS IN THE RAT.

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J Endocrinol; 93(1):11-16 1982

The effect of chronic administration of a high dose of estradiol benzoate (OB) on growth and prolactin receptor content of the N-nitrosomethylurea (NMU)-induced rat mammary tumor was investigated. Daily im administration of 50 ug OB for 8 days to tumor-bearing rats induced marked reduction in tumor size which was already significant after only three injections. Simultaneous daily administration of 1 mg perphenazine to stimulate endogenous prolactin release counteracted the inhibitory effect on tumor growth of OB but only partially since the tumors grew significantly more when perphenazine was injected alone. No treatment significantly affected prolactin receptor content in the tumors. We concluded that administration of pharmacological doses of OB has a potent antitumor action on the NMU-induced rat mammary tumor. This effect can only partially be explained by inhibition of the peripheral action of prolactin. (Author abstract) (22 Refs)

91. PROGESTIN- AND ANDROGEN-BINDING COMPONENTS IN A HUMAN GRANULOSA-THECA CELL TUMOR.

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Gynecol Oncol; 13(3):309-317 1982

Macromolecules which bound progesterone (P), medroxyprogesterone acetate (MPA), and dihydrotestosterone (DHT) have been identified in the cytoplasmic fraction of a human granulosa-theca cell tumor and partially characterized. Bound [3H]P sedimented at the 3.6 S region of the sucrose gradients, whereas bound [3H]MPA was observed mainly in the 6 S region. P and MPA competed with each other for binding to these components. The specific MPA-binding sites were saturable and had a Ka of 3.6 nM-1. Heating the tumor cytosol at 37 C for 10 min diminished its progestin-binding activity. The DHT-binding components had sedimentation coefficients of 4.2 S and 6 S, and a Ka of 0.4 nM-1. They were heat sensitive and were precipitable by protamine sulfate. Attempts to demonstrate specific binding of estrogens and glucocorticoids by this tumor cytosol were unsuccessful. (Author abstract) (28 Refs)

92. ENHANCED AND REVERSED GROWTH IN VIVO OF A PREGNANCY-DEPENDENT MOUSE MAMMARY TUMOR (TPDMT-4) BY A GONADOTROPIN-RELEASING HORMONE AGONIST ANALOG.

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Eur J Cancer Clin Oncol; 18(5):495-505 1982

TPDMT-4 pregnancy-dependent mammary tumors grow continuously in DDD female mice carrying pituitary isografts (PI) ectopically or bearing an sc 17beta-estradiol plus progesterone (EP) pellet. A gonadotropin-releasing hormone (GnRH) agonist (D-leucyl6, des-glycyl-NH210, prolyl-ethylamide9) GnRH (TAP-144), was examined for its antitumor activity in these experimental systems. TAP-144 was injected ip at doses of 300 and 600 ug 6x weekly, when tumors grew to significant sizes. TAP-144 enhanced tumor growth during the first 2 weeks and subsequently reversed it in a dose-related manner in PI-bearing mice. The agonist did not affect tumor growth in the absence of ovaries in these mice. In ovariectomized mice, TAP-144 enhanced EP pellet-induced tumor growth but never reversed it. In ovariectomized, PI-bearing mice. TAP-144 first enhanced and subsequently reversed tumor regrowth induced by ovarian grafts to a greater extent when commencing it simultaneously with ovarian grafting than 30 days before it. The agonist also exerted the dual effects on TPDMT-4V ovarian-dependent subline tumors in the absence of PI. In TAP-144-treated mice, enhanced tumor growth was related to many solid corpora lutea in ovaries and fully developed mammary glands, but reversed growth was related to atrophied luteal components and mammary glands. The results suggest that TAP-144 enhances tumor growth first via its stimulative action on the pituitary-ovarian axis and causes tumor regression later via its direct inhibitory action on ovaries. (Author abstract) (31 Refs)

93. HISTOAUTORADIOGRAPHY IN EVALUATION OF TUMOR-SEEKING PROPERTIES OF RADIONUCLIDES.

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Med Radiol (Mosk); 27(5):15-20 1982

Tumor-seeking properties of various radionuclides were studied in random-bred male rats bearing implanted sarcoma 45 (spindle cell sarcoma), Guerin carcinoma (poorly differentiated uterine carcinoma), or hepatoma 27 (poorly differentiated liver tumor). The tumor-bearing animals were inoculated with 111In-citrate, 111In-bleomycin, 67Ga-citrate, 99mTc-citrate, or 99mTc-pertechnetate; 4-24 hr after radionuclide administration, the animals were sacrificed, and specimens of tumor and normal tissue were subjected to histoautoradiographic analysis. Comparative evaluation of tumor-muscle, tumor-blood, and tumor-liver coefficients for the five radionuclides tested showed that all except the 99mTc-citrate met the requirement of selective accumulation. Gallium and indium compounds were more effective in visualization of tumors located above the diaphragm, while 99mTc-pertechnetate was more effective in visualization of tumors located below the diaphragm. (7 Refs) (In RUS)

94. BIOCHEMICAL PHARMACOLOGY AND TOXICOLOGY OF 8-AZAADENOSINE AND FORMYCIN ALONE AND IN COMBINATION WITH 2'DEOXYCOFORMYCIN (PENTOSTATIN) (MEETING ABSTRACT).

Spremulli EN, Dexter DL, Farineau DM, Diamond I, Crabtree GW, Ghoda L, McGowan D, Parks RE, Calabresi P
Roger Williams General Hospital and Brown University, Providence, RI, 02912
Proc Am Soc Clin Oncol; 1:C-78 1982

The growth inhibitory effects of the candidate antineoplastic agents 8-azaadenosine (8-azaAdo) and formycin (Fmy) against cultured human colon cancer cells are markedly potentiated by pretreatment of the cultured cells with the adenosine deaminase inhibitor 2'-deoxycoformycin (dCF). Thus it was of interest to examine the toxicology and metabolism of 8-azaAdo and Fmy both as single agents and in combination with dCF. The LD10 values (mice) for 8-azaAdo and Fmy given ip on qd x 5 schedule were 30 and 21 mg/kg respectively. With 0.1 or 1 mg/kg of dCF given 1 hr prior to 8-azaAdo or Fmy, the LD10 dose was reduced to 10 mg/kg for both drugs. The dose limiting organ toxicity for both agents either alone or in combination with dCF was hepatic; bone marrow cellularity was only slightly altered at the LD10 doses. 8-azaAdo and Fmy nucleotides were detected in the livers of treated mice by high performance liquid chromatography. After 2 hrs of incubation with 1 mM of either analog, isolated rat hepatocytes accumulated 2.2 umol 8-azaATP/gm of cells or 4.0 umol FmyTP/gm of cells. When rat hepatocytes were preincubated in vitro with dCF (1 ug/ml) levels of 8-azaATP or FmyTP increased approximately two-fold. ATP levels decreased to below the limits of detection in cells treated with either combination (control values, 1.5 umol/gm cells). (no Refs)

95. DIFFERENTIAL MECHANISM OF DNA SYNTHESIS INHIBITION IN VITRO FOR N-TRIFLUOROACETYLADRIAMYCIN-14-VALERATE (AD 32) AND ADRIAMYCIN (ADR) (MEETING ABSTRACT).

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Division of Pharmacology, Sidney Farber Cancer Institute, Boston, MA, 02115
Proc Am Assoc Cancer Res; 23:675 1982

In vitro, at equimolar concentrations (10 uM) or at concentrations related to their 50% growth-inhibitory values (1 uM ADR vs 4.8 uM AD 32), AD 32 is consistently more inhibitory than ADR of DNA synthesis in CCRF-CEM (human lymphoblastic leukemic) cells, as measured by the incorporation of [3H]-thymidine (Tdr) into acid-precipitable fractions. While the inhibitory activity of ADR gradually rises from 45% at 15 min to 76% at 3 hr, the strong inhibitory effect of AD 32 is already evident at the earliest timepoint studied (86% at 15 min), with relatively little change over the next 3 hr. For ADR, DNA complexation synthesis inhibition is known to be the result of drug-DNA complexation, an effect not possible with the non-DNA binding AD 32. We now find that the inhibition of DNA synthesis in CEM cells is the result of impaired intracellular transport of Tdr. Thus, CEM cells at 0 degree take up Tdr (determined in the acid-soluble fraction), but do not incorporate the base into DNA. Incubation of cells at 37 degrees for 1 hr in the presence of AD 32 (0.1, 1, 5, 10, or 20 uM), followed by 1 hr exposure to labeled Tdr at 0 degrees in fresh medium, results in significantly decreased levels of radioactivity in acid-soluble fractions compared to untreated controls. In contrast, little inhibition of Tdr uptake is seen with ADR across the same dosage range under these conditions. (1 Ref)

96. COLLATERAL SENSITIVITY OF PALA IN P388 TUMOR RENDERED RESISTANT TO ACIVICIN (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:29 1982

PALA, N-(phosphonacetyl)-L-aspartic acid, is ineffective in treating mice bearing the parent P388 leukemia lines; an increased life span (ILS) of 9 percent above control. However, such treatment becomes highly effective when the parent P388/0 leukemia line has been rendered resistant to another antimetabolite, Acivicin, an ILS of 91 percent above control. PALA treatment did not inhibit carbamyl phosphate synthetase (CPSII) of P388/0 line, whereas a similar treatment produced 35% inhibition of CPS II activity in P388/ACIA, a PALA sensitive line. Aspartate transcarbamylase was inhibited approximately by 80 percent in both tumors following PALA therapy. PALA treatment of P388/ACIA animal bearing tumors demonstrated that the specific activities of cytidine, uridine, thymidine, deoxyuridine and dexcycytidine nucleoside kinases (pyrimidine salvage enzymes) were inhibited 60.7, 59.6, 43.5, 72.9 and 33.6 percent of saline control respectively, whereas a similar treatment of P388/0 tumor bearing showed 0, 11, 20.4, 0, 0 inhibition of the enzymes respectively. A similar examination of purine salvage enzymes (APRTase, HPRTase) following PALA therapy demonstrated 61.8, 70 percent inhibition respectively in P388/ACIA, whereas in P388/0 PALA treatment produced no inhibition. Twenty-four hr following administration of PALA, 200 mg/kg ip to tumor-bearing mice, the intracellular concentration of the pyrimidine nucleoside triphosphate was decreased in the P388/ACIA, PALA sensitive cells, by 62.3% as compared to a 16.5% reduction in P388/0, PALA resistant line. Moreover, the purine nucleotide pool demonstrated 132% increase in P388/ACIA line, no such increase was seen in P388/0 line. (no Refs)

97. BLEOMYCIN HYDROLASE ACTIVITY AND CYTOTOXICITY IN HUMAN TUMORS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:22 1982

BLM Bleomycin hydrolase, an aminopeptidase B-like enzyme activity, inactivates BLM. To test the importance of this enzyme activity in limiting the therapeutic effectiveness of BLM, we measured BLM hydrolase activity and response to BLM in human pelvic tumors. Portions of benign (schwannoma) and malignant (ovarian, cervical and colonic) human tumors were homogenized with 0.1 M phosphate buffer and centrifuged at 20,800xg for 45 min. The supernatant fraction was centrifuged at 105,000 xg for 1 hr and low molecular weight material removed from the resulting supernatant fraction with a CF-25 Centriflo cone. The BLM hydrolase activity was then determined using 50 ug/ml of BLM B2 and a sensitive new high pressure liquid chromatography technique. The remaining portion of the human tumor was dissociated to form a single cell suspension and exposed to 0.05 or 1 ug/ml of BLM for 1 hr. Cells were then placed in soft agar and colony formation was determined 3 wk later and compared to that of untreated cells. BLM hydrolase activities varied more than 5-fold in individual tumors and the response to BLM varied more than 100-fold. No correlation was observed between response to BLM and BLM hydrolase activity. Thus, we have established that human tumors can inactivate BLM and conclude that either (a) the BLM hydrolase activity of clonogenic cells from human tumors examined was significantly different from the nonclonogenic cells or (b) other mechanisms of resistance must be operative. (no Refs)

98. INDUCED RESISTANCE IN LEUKAEMIA L1210 TO ADRIAMYCIN AND ITS CROSS-RESISTANCE TO VINCRISTINE AND BOUVARDIN.

Chitnis MP, Joshi SS, Gude RP, Menon RS
Chemotherapy Div., Cancer Res. Inst., Parel, Bombay 400 012, India
Chemotherapy; 23(3):209-212 1982

The induction of complete resistance to adriamycin in L1210 leukemia was accomplished after 10 transplant generations. The adriamycin-resistant subline showed cross-resistance to vincristine and bouvardin. It was sensitive to methotrexate; this was observed by a 50% increase in life span compared to th life span of untreated control animals. (Author abstract) (18 Refs)

99. QUANTITATIVE ANALYSIS OF THE CYTOKINETIC RESPONSE OF KHT TUMORS IN VIVO TO 1-BETA-D-ARABINOFURANOSYLCYTOSINE.

Pallavicini MG, Gray JW, Folstad LJ
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Cancer Res; 42(8):3125-3131 1982

Quantitative estimates of cytokinetic perturbations induced over a 30-hr interval in KHT tumor cells in vivo by a single dose of 1-beta-D-arabinofuranosylcytosine (ara-C) were inferred from measurements of DNA distribution sequences, tritiated thymidine incorporation into tumor cell DNA, and radioactivity of cells labeled with tritiated thymidine prior to treatment with ara-C. These data were analyzed collectively to produce a mathematical model describing the effects of ara-C on tumor cell cycle kinetics. During analysis, we postulated that ara-C produced a transient block at the a G1-S-phase boundary, that ara-C killed all cells in S phase, and that the cells killed by ara-C did not cycle after treatment. The analysis showed that the duration of the G1-S-boundry block was 5.5 hr, that cells were recruited from G0 into cycle beginning 5.5 hr posttreatment, and that the G1, S, and G2M phase durations of the clonogenic cells which were initially 2, 11.5, and 2 hr, respectively, changed to 0.8, 4.6, and 0.8 hr at 14 hr posttreatment. Cells killed by ara-C were removed from the tumor beginning 10 hr posttreatment. We then used the mathematical model to predict clonogenic tumor cell survival following a second dose of ara-C administered at time intervals ranging from 1 to 30 hr after the first treatment. Clonogenic tumor cell survival following the second dose of ara-C was then experimentally determined and agreed well with the model predictions. (Author abstract) (22 Refs)

100. INDUCTION OF RETROVIRUS GENE EXPRESSION ON MOUSE CELLS BY SOME CHEMICAL MUTAGENS.

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Cancer Res; 42(8):3050-3055 1982

Cell cultures derived from a variety of mouse strains were compared for their relative capacity to be induced to express endogenous retrovirus proteins by exposure to 5-diododeoxyuridine under optimized experimental conditions. Induction frequencies varied between 6.0 x 10(-1) and 1.7 x 10(-2) with AKR cells showing the highest capacity and C57BL/6 x C3H F1 cells the lowest. Virus expression was induced in AKR cells with other chemical mutagens of the polyaromatic hydrocarbon [benzo(a)pyrene and phenol, diol, and epoxide metabolites] and nucleoside analog classes, but alkylating agents were inconsistent or failed to induce. Considerable differences in the efficiency of induction were seen between various halogenated nucleosides, while under these conditions the nucleoside 5-azacytidine induced greater than 90% of AKR cells at a concentration of 2 to 4 ug/ml. The high frequency of induction by 5-azacytidine, relative to other nucleoside analogs, and the absence of induction by other mutagens further indicate that endogenous virus induction occurs via nonmutagenic mechanisms and that some mutagens may also affect regulatory functions independent of their mutagenic action. (Author abstract) (42 Refs)

101. QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS OF PURINES II: PREDICTION OF ACTIVITY AGAINST ADENOCARCINOMA CA755 AND TOXICITY IN MICE.

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J Pharm Sci; 71(6):618-620 1982

Quantitative structure-activity relationships (QSAR) were derived for a number of 2,6-mono- and disubstituted purines. The derived equations relate the anticancer activity in murine Adenocarcinoma CA755 to the molar refractivity of substituents at position 2 and electron-withdrawing effects of substituents at position 6. A QSAR was also derived for the acute toxicity (LD50) of substituents at position 6. The results suggest that toxicity is relatively independent of the nature of the substituent. (Author abstract) (20 Refs)

102. EFFECT OF TOCOPHEROL (VITAMINE E) ACID SUCCINATE ON GROWTH AND MORPHOLOGY OF MOUSE MELANOMA AND MOUSE NEUROBLASTOMA CELLS IN CULTURE (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:900 1982

Vitamin E acid succinate (5 ug/ml) induced morphological alterations (increases in size, long cytoplasmic processes, parallel arrangement of cells) and growth inhibition in mouse melanoma (B-16) cells in culture, but it causes only growth inhibition with enlargement of cells in mouse neuroblastoma (NBP2) cells in culture. Vitamin E acid succinate at a similar concentration was ineffective in mouse fibroblasts (L-cells) in culture. The effects of vitamin E acid succinate were mostly irreversible; however, partially affected cells and vitamin E-resistant cells exist in culture. These cells eventually reach confluency. The addition of sodium succinate with an equivalent volume of ethanol or other forms of vitamin E such as aquasol DL-alpha-tocopherol acetate, DL-alpha-tocopherol nicotinate and DL-alpha-tocopherol free alcohol at a similar concentration was ineffective. The solvents for aquasol vitamin E acetate and vitamin E free alcohol at higher concentrations were toxic; therefore, these forms of vitamin E were considered not suitable for an in vitro study. The effects of vitamin E acid succinate were also expressed in hormone supplemented serum free medium (SFM); however, the concentrations needed to produce changes in SFM were 5 to 10 times less than that needed in serum supplemented medium. Vitamin E also modifies the effect of several tumor therapeutic agents such as cyclic AMP stimulating agents, vincristine, 5-fluorouracil, adriamycin, bleomycin, cis-platinum, and x-irradiation. The extent of modification depends upon the cell type, and particular agent. (no Refs)

103. DECREASE OF TUMOR GROWTH IN MICE AFTER INTRAVENOUS THYMOSIN-TREATED BONE MARROW CELL INJECTION.

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JNCI; 69(1):27-31 1982

The effect of iv injection in C57BL/6 mice of 3 x 10(7) bone marrow cells preincubated in either thymosin fraction V or thymosin alpha-1 was evaluated on the growth of a 3-methylcholanthrene-induced transplantable tumor in a syngeneic system. The effect was then compared to that elicited by theophylline or levamisole, which both demonstrated thymosin-like action in vitro. The results showed significantly retarded tumor growth (P less than 0.001) and prolonged survival time (P less than 0.001) when thymosin fraction V was used. The same results were obtained with thymosin alpha-1 with use of the same protocol but only one-twentieth of the concentration of fraction V. Theophyline and levamisole demonstrated no antitumor effect. (Author abstract) (42 Refs)

104. REGULATION OF HUMAN NATURAL KILLING BY LEVAMISOLE.

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Cancer Immunol Immunother; 13(1):24-29 1982

Effect of levamisole (LE) on human natural killing (NK) activity was studied in vitro. LE at concentrations greater than 10(-4) M clearly inhibited NK activity. Peripheral blood leukocytes (PBL) were pretreated with LE for 18 hr, washed free of the reagent, and then tested for NK activity. PBL pretreated with LE at concentrations greater than 10(-4) M again showed decreased NK activity, even though LE was not present during the NK assay suggesting that LE inhibited NK by decreasing effector cell activity, without affecting target cell susceptibility. The susceptibility of K562 to killing by complete medium (CM)-treated PBL or LE-treated PBL was, however, unaffected by LE treatment. The kinetics of effector cell inactivation was assessed by preincubating several aliquots of the same PBL effector cell preparation for a total period of 16 hr. Results of the experiment showed that greater than 4 hr was required to inactivate NK effector cells, if the activity was subsequently tested in the absence of the drug. Presence of 10(-3) M LE throughout the entire culture period depressed PBL response to phytohemagglutinin (PHA) stimulation. A 19-hr pretreatment with a subsequent wash had no effect on the response to PHA, while NK activity was greatly suppressed by the treatment. PBL were pretreated with LE and cultured in CM. PBL preincubated with 10(-3) M LE for 8 hr showed suppressed NK activity, as expected, when tested immediately after the preincubation. When the inactivated effector cells were incubated further for an additional 16 hr, the activity recovered to near-normal level. Therefore, the inactivation was reversible. (31 Refs)

105. IN VIVO MACROPHAGE-MEDIATED TUMOR CYTOTOXICITY IN THE MOUSE.

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Immunol Lett; 4(6):321-325 1982

Immunological activity of mouse peritoneal macrophages was studied in vivo in the presence and absence of lipopolysaccharide (LPS). LPS-activated macrophages acquired enhanced cytotoxicity for the DBA/2 mastocytoma (P815) cells at an effector:target ratio (ETR) of 25:1. The suppressive activity of control macrophages, LPS-activated macrophages, and dead control macrophages was compared with that of the animals receiving no macrophage treatments. No difference in tumor size could be demonstrated in any of the five groups of DBA/2 mice, 12 days after injection of the P815 cells. By day 17, the tumors in the mice treated with either control or activated macrophages at a 20:1 ratio had decreased in size. When the mice were injected with control or activated macrophages at the lower ETR of 10:1, the tumors increased slightly in size or remained the same as when measured on day 12. The mean survival time for the animals treated with LPS-activated macrophages at ETR of 20:1 (32 +-3.9 days), or control macrophages at ERT of 10:1 (30.7 +-2.96), or 20:1 (31.8 +-3.7 days) was longer than that for untreated control animals (21.2 +-2.2 days), whereas the mice treated with LPS-activated macrophages at ERT 10:1 (24.2 +-2.94 days) did not differ significantly from controls. Results showed that tumor cell growth can be slowed down in vivo when either LPS-activated or non-activated macrophages are injected into the site of the tumor mass. More LPS-activated macrophages than non-activated macrophages are required to inhibit tumor growth. (20 Refs)

106. DIFFERENT STRUCTURAL REQUIREMENTS OF ENDOTOXIC GLYCOLIPID FOR TUMOR REGRESSION AND ENDOTOXIC ACTIVITY.

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Dept. Biochemistry, Hirodaki Univ. Sch. Medicine, Hirosaki 036, Japan
Biochem Biophys Res Commun; 106(3):677-682 1982

Chromatographic separation of a mixture of glycolipids obtained by hydrolysis of endotoxins from Salmonella typhimurium with HCl into toxic and nontoxic fractions possessing tumor regressive activity is reported. The endotoxic glycolipids (ReGL) were treated with sodium acetate, mild HCl (0.1 N) and sodium hydroxide (0.1 N) and their biological activities were determined. Hydroxyl aminolysis resulted in loss of both tumor regressive activity and toxicity, indicating that such activities depend at least partially on the presence of the O-ester bound fatty acids. Treatment with sodium acetate removed 97% of the 2-keto-3-deoxyoctonate (KDO) while treatment with mild acid removed KDO plus phosphorus. The presence of KDO was not essential for both toxicity and tumor regressive activity, while the presence of a phosphate group occupied at a particular position was essential for toxicity. This phosphate was thought to be linked at the reducing end of the glucosamine residue and was not required for tumor regression activity. When ReGL-HCl was separated by preparative thin layer chromatography into three different multiple band fractions, all the fractions possessed tumor regressive activity similar to ReGL, but differed in toxicity. It was concluded that minute quantities of toxic components were contaminating two of the fractions. Thses findings confirm that t chemical structures of the glycolipids essential for tumor regressive activity and toxicity are different. (14 Refs)

107. LACK OF INFLUENCE OF S-ADENOSYL-L-METHIONINE (SAME) TREATMENT ON WALKER 256/B CARCINOMA AND SAME TURNOVER IN RATS.

Pezzoli C, Gualtani A, Villa P, Bartosek I, Stramentinoli G
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Toxicol Lett; 12(2/3):207-213 1982

The effect of S-adenosyl-L-methionine (SAMe) treatment on tumor growth, cachexia and anorexia in male Sprague-Dawley rats transplanted with Walker 256/B carcinoma was investigated and SAMe levels and turnover in liver, kidney, and neoplastic tissue were determined. Normal and carcinoma-bearing rats received 10 uCi (specific activity 54 mCi/millimole) L-[methyl-14C]-methionine on day 10 after transplantation. Tissue levels of SAMe were determined at 5, 10, 15, 30, and 60 min after methionine treatment. SAMe soln (20 mg/kg) was injected sc at a dose of 20 mg/kg bid from day 1 of tumor transplantation. SAMe treatment did not affect mean survival time of tumor-bearing rats, did not significantly alter the time course of body wt in normal and tumor-bearing animals, and did not change total food intake during the 15-day survival period. Tumor wt were similar in treated and untreated groups. During tumor growth, SAMe treatment did not affect spleen and liver wt. Specific activity of SAMe in the liver was lower in control than in tumor-bearing rats, the difference being significant at 15, 30, and 60 min after administration. However, the levels of SAMe in the liver of tumor-bearing rats were significantly lower than those in controls, compensating for the higher radioactivity found in the host liver. Thus, tumor implantation does not modify SAMe metabolism in the host, and the exogenously supplied SAMe does not interfere with tumor growth in rats. (29 Refs)

108. TEMPERATURE DEPENDENCE AND EFFECT OF MEMBRANE LIPID ALTERATION ON MELPHALAN TRANSPORT IN L1210 MURINE LEUKEMIA CELLS.

Burns CP, Dudley DT
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Biochem Pharmacol; 31(11):2116-2119 1982

The effects of temperature and lipid composition of cell phospholipids on the transport of melphalan (MP) were examined in L1210 lymphoblastic leukemia cells from male DBA/2 mice fed either sunflower seed oil or coconut oil diets. The transition temperature for MP transport by cells from mice fed the sunflower seed oil diet, which was rich in polyunsaturates, was 18.7 +-0.5 C. In contrast, the transition temperature was 22.5 +-1.2 C for cell from animals fed the coconut oil diet. The 3.8 C difference associated with the lipid alteration seems to reflect a lipid phase change. The lower transition temperature for MP transport agreed with the transition temperature for electron spin resonance studies, providing more evidence that the break in the Arrhenius plot for MP transport by the L1210 cells is probably due to a lipid phase change. No differences in the maximal velocity or Michaelis constant were observed for MP transport in mice fed the sunflower seed oil or coconut oil diets. The results indicated that the discontinuity in the Arrhenius plot was the result of lipid phase transition and not of an interaction of the two carrier-mediated transport processes. (11 Refs)

109. IDENTIFICATION OF METABOLITES OF 9-BETA-D-ARABINOFURANOSYL-2-FLUOROADENINE, AN ANTITUMOR AND ANTIVIRAL AGENT.

Struck RF, Shortnacy AT, Kirk MC, Thorpe MC, Brockman RW, Hill DL, El Dareer SM, Montgomery JA
Southern Res. Inst., 2000 9th Ave. South, Birmingham, AL, 35255
Biochem Pharmacol; 31(11):1975-1978 1982

Analysis of blood from a dog given a 400 mg/m2 dose of 9-beta-D-arabinofuranosyl-2-fluoroadenine (2-F-araA) led to the identification of parent drug and a major metabolite, 9-beta-D-arabinofuranosyl-2-fluorohypoxanthine. 2-Fluoroadenine, a toxic derivative of 2-F-araA, was not detected in blood within the limits of detection, suggesting that parent drug was absorbed and distributed without systemic exposure to this toxic derivative. Parent drug, 2-fluoroadenine, and 9-beta-D-arabinofuranosyl-2-fluorohypoxanthine were identified in urine of dog, monkey, and mouse. (Author abstract) (15 Refs)

110. DIURNAL VARIATION IN METHYLPREDNISOLONE METABOLISM IN THE RAT.

English J, Marks V
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IRCS Med Sci [Cancer]; 9(8):721 1981

The diurnal variation in the pharmacokinetics of methylprednisolone (MP) was investigated in male Norwegian hooded rats injected with 1 mg MP/kg body wt into the femoral vein. Plasma half lives at 0,000 0,600, 1,200, and 1,800 hr were 20.4 +-0.4 min, 18.0 +-1.4 min, 10.8 +-0.9 min, and 32.5 +-1.5 min, respectively. The max half life (at 1,800 hr) corresponded closely to the time of max cure rate of murine leukemia and of minimum drug-associated mortality caused by a combination of cytotoxic drugs. (5 Refs)

111. CLONAL VARIATION IN THE SENSITIVITY OF B16 MELANOMA TO M-AMSA.

Stephens TC, Peacock JH
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Br J Cancer; 45(6):821-829 1982

A hypothesis that m-AMSA may have greater cytotoxicity in melanin-containing tumor tissues, because it may reversibly bind to melanin, leading to prolonged drug exposure, was examined. Clonal lines of B16 melanoma which differed widely in pigmentation level were selected by isolating artificial lung colonies and in vitro soft-agar colonies, and implanting them into mice. Excision cell-survival assays performed 24 hr after drug administration showed that in vivo sensitivity to m-AMSA progressively increased as pigmentation level decreased, but that m-AMSA drug levels measured 24 hr after treatment were much lower in amelanotic than in melanotic lines. In dose-survival studies the reduced sensitivity of melanotic cell lines was revealed as a large shoulder (Dq = 27 mg/kg) though the terminal slopes for melanotic and amelanotic cell lines were similar (D10-approx 31 mg/kg). Time-course studies indicated that there was no significant loss of drug from a melanotic cell line for 72 hr after drug administration, though in an amelanotic cell line drug levels fell 10-fold in 10 hr. There was, however, no evidence for prolonged drug cytotoxicity in the melanotic cell line. Using a fractionated drug-treatment regime, the greater cytotoxicity of m-AMSA to amelanotic tumor tissue was confirmed in a non-invasive regrowth-delay assay. (Author abstract) (15 Refs)

112. COMPARATIVE STUDIES OF AROMATASE INHIBITORS IN CULTURED HUMAN BREAST CANCER CELLS.

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Cancer Res; 42(8,Suppl):3378s-3381s 1982

The presence of aromatase activity, estrogen receptors, and estrogenic responsiveness in MCF-7 human breast cancer cells has allowed this cell line to be used as a unique in vitro system for investigating the biological activities of potentially therapeutic aromatase inhibitors. We now report the results of studies which have examined the cytotoxicity, antiaromatase, and intrinsic estrogenic activities of aminoglutethimide, 1,2-dehydrotestolactone (testolactone), dihydrotestosterone, 4-hydroxy-4-androstene-3,17-dione, and 10-propargylestr-4-ene-3,17-dione within MCF-7 monolayer cultures. Cell viability was determined by trypan blue exclusion, and aromatase activity was assessed by quantifying the amounts of [3H]estradiol formed from [3H]testosterone. Estrogenic activity was assessed by examining the ability of each inhibitor to increase cytoplasmic progesterone receptor and deplete cytoplasmic estrogen receptor concentrations in these cells during a 5-day incubation period. Cytoplasmic progesterone and estrogen receptors were measured by the single-saturating-dose technique using [17alpha-methyl-3H]-17alpha,21-dimethyl-19-norpregna 4,9-diene-3,20-dione and [3H]estradiol as the labeled ligands for each assay, respectively. The results showed that all of these compounds were noncytotoxic aromatase inhibitors in MCF-7 cells but that these agents demonstrated marked differences in inhibitory potency (10-propargylestr-4-ene-3,17-dione greater than 4-hydroxy-4-androstene-3,17-dione much greater than dihydrotestosterone much greater than testolactone = aminoglutethimide). The incubation of cells with 4-hydroxy-4-androstene-3,17-dione resulted in cytoplasmic progesterone and estrogen receptor responses that were similar in magnitude to those observed in other cultures incubated with equimolar concentrations of estradiol. None of the other four agents demonstrated estrogenic activity in this system. However, we have previously observed that dihydrotestosterone has substantial antiestrogenic action in this system. Taken together, these results indicate that some aromatase inhibitors may influence the hormonal regulation of human breast cancer cells by more than one mechanism. (Author abstract) (12 Refs)

113. A NEW HYPOTHESIS BASED ON SUICIDE SUBSTRATE INHIBITOR STUDIES FOR THE MECHANISM OF ACTION OF AROMATASE.

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Cancer Res; 42(8,Suppl):3327s-3333s 1982

Recently, it was discovered that 4-hydroxy-4-androstene-3,17-dione, 4-androstene-3,17-trione, and 1,4,6-androstatriene-3,17-dione, compounds previously reported to be competitive inhibitors of aromatase, cause a time-dependent loss of aromatase activity in human placental microsomes. We report here that 1,4-androstadiene-3,17-dione (Ki 0.32 uM; Kinact 0.91 x 10(-3)/sec) and testolactone (Ki 35 uM; Kinact 0.36 x 10(-3)/sec) also cause a similar loss of aromatase activity. The mechanism which explains the unexpected loss of activity caused by these five inhibitors is neither established nor apparent from current theories of the enzyme mechanism of action of aromatase. We propose an inactivation mechanism based on a new hypothesis for estrogen biosynthesis in which the third enzyme oxidation carried out by aromatase results in the formation of an enzyme-bound intermediate. This intermediate is released as an aromatized product via a facile elimination reaction which simultaneously regenerates the unaltered active enzyme. Various structural modifications made in these five inhibitors are hypothesized to redirect this elimination reaction so that the steroid intermediate remains covalently attached to the enzyme instead of being released as an aromatized product. (Author abstract) (24 Refs)

114. OVERVIEW OF RECENT DEVELOPMENT OF AROMATASE INHIBITORS.

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Cancer Res; 42(8,Suppl):3312s-3314s 1982

Since the first publication in 1973 concerning aromatase inhibitors, several effective compounds have been reported by a number of investigators. Our studies with 4-hydroxyandrostene-3,17-dione, 4-acetoxyandrostene-3,17-dione, and 1,4,6-androstatrienedione indicate that these compounds cause rapid competitive inhibition of the enzyme. Aminoglutethimide binds competitively to cytochrome P-450 and inhibits a number of steroid hydroxylations but is more active as an aromatase inhibitor. 16alpha-Bromoandrogens and 7alpha-(4'-amino)phenylthioandrostenedione are also reported to be aromatase inhibitors. As yet, only some of these compounds have been evaluated in vivo, but all appear to be similarly effective in inhibiting aromatization in breast tumors in vitro. Recent interest has focused on enzyme inactivators or 'suicide' inhibitors. Such compounds act as substrates for the enzyme but are converted by the normal catalytic mechanism of the enzyme to reactive intermediates. These then bind covalently to the active site of the enzyme causing loss of activity. Active site-directed inhibitors are usually quite specific and have long-lasting effects in vivo. A number of new compounds, as well as some of the above compounds, appear to be inactivators of aromatase and are potentially interesting as agents for hormone-dependent breast cancer therapy. (Author abstract) (42 Refs)

115. DRUG ACTIVITY AND THERAPEUTIC SYNERGISM IN CANCER TREATMENT.

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Cancer Res; 42(8):2963-2971 1982

In work involving modeling of response surfaces to describe the effects of cancer chemotherapy treatments, it is important to define activity and therapeutic synergism in a statistically defensible manner. This requires the construction of confidence intervals around the estimated optimal treatment which has been achieved by use of an indirect method first proposed by Box and Hunter. Activity for a drug or a combination can be claimed at 100(1-alpha)% level of confidence when the 100(1-alpha)% confidence interval about the optimal treatment excludes a zero dose. Results of treatment of B16 melanoma and Lewis lung carcinoma with 3,4-dihydroxybenzohydroxamic acid are used to demonstrate this definition. Extensions of this concept lead to a statistically valid definition of therapeutic synergism. If the confidence region about the optimum combination of k drugs does not contact any of the k -1 dimensional subspaces, then a k drug therapeutic synergism can be claimed. In the event that a k drug therapeutic synergism cannot be claimed, there may be subsets of the drugs which do combine with therapeutic synergy. These concepts are demonstrated by two- and three-drug combination experiments in L1210-bearing C57BL/6 x DBA/2 F1 (B6D2F1) mice. Razoxane and dacarbazine show therapeutic synergism at a 95% confidence level. A three-drug combination of 5-fluorouracil, Teniposide, and mitomycin C is considered. In this case, although the estimated optimum treatment includes 48.1 mg of 5-fluorouracil per kg, 15.9 mg of Teniposide per kg, and 3.9 mg of mitomycin C per kg, the confidence region generated failed to confirm at an 80% level of confidence that 5-fluorouracil was a necessary component of the best treatment. (Author abstract) (15 Refs)

116. INHIBITION OF CARCINOGENESIS OF THE RAT MAMMARY GLAND AND MOUSE URINARY BLADDER BY A RETINOID AND AN INDUCER OF INTERFERON SYNTHESIS (MEETING ABSTRACT).

McCormick DL, Becci PJ, Moon RC
Illinois Institute of Technology Research Institute, Chicago, IL, 60616
Proc Am Assoc Cancer Res; 23:354 1982

Retinoids are potent inhibitors of chemical carcinogenesis of the mammary gland and urinary bladder in experimental animals. MVE-2 is a divinyl ether-maleic anhydride copolymer which induces interferon synthesis. These studies were conducted to determine the influence on chemical carcinogenesis of combined administration of MVE-2 and the retinoid N-(4-hydroxyphenyl)retinamide (4-HPR). In the mammary study, virgin female Sprague-Dawley rats received a single iv dose of 20 mg N-methyl-N-nitrosourea per kg body weight. In the bladder study, male C57BL/6 x DBA-2 F1 mice received 8 weekly ig doses of 7.5 mg (4-(butylnitrosoamino)-1-butanol). One week after the final carcinogen treatment, animals in both studies were randomized into groups of 50 as follows: (1) placebo diet (2) 4-HPR, 391 mg/kg diet (3) MVE-2, 25 mg/kg body weight, administered ip in 4 week cycles (3 weeks treatment, 1 week rest) throughout the study (4) MVE-2, 12.5 mg.kg, given as above (5) 4-HPR diet +— 25 mg MVE-2/kg (6) 4-HPR diet + 12.5 mg MVE-2/kg. In both studies, 4 HPR (group 2) and the high dose MVE-2 (group 3) treatments resulted in a significant inhibition of carcinogenesis. The low dose of MVE-2 (group 4) was not active in chemoprevention. No synergistic or additive interaction was observed between 4-HPR and MVE-2 at either dose level. These data suggest that either 4-HPR and MVE-2 inhibit carcinogenesis by a common mechanism, or, more likely, that the compounds have an antagonistic activity which precludes an additive or synergistic interaction in cancer inhibition. (no Refs)

117. MODIFYING EFFECT OF VINBLASTINE ON SUPEROXIDE ANION PRODUCTION BY MEMBRANE PERTURBING AGENTS IN POLYMORPHONUCLEAR LEUKOCYTES.

Okamura N, Ishibashi S
Dept. Physiological Chemistry, Hiroshima Univ. Sch. Medicine, Minami-ku, Hiroshima, Hiroshima 734, Japan
J Biochem (Tokyo); 91(5):1725-1730 1982

Superoxide anion production in peritoneal polymorphonuclear leukocytes obtained from guinea pigs was stimulated by in vitro treatment with membrane-perturbing agents, such as cytochalasin D, concanavalin A, phorbol myristate acetate, myristate, digitonin, and NaF. Vinblastine modified these stimulating effects on the superoxide anion production, but its modifying effect was not uniform. The effect of cytochalasin D was stimulated by vinblastine at the concentration of 10(-5)-10(-7) M, whereas it was inhibited at the concentration of 10(-4) M. At 10(-4)-10(-5) M, vinblastine was inhibitory to the effect of concanavalin A, and lower concentrations had no significant effect. Stimulation of the superoxide anion production by phorbol myristate acetate and myristate was further enhanced by vinblastine at any concentration in the range of 10(-4)-10(-8) M with peaks at 10(-6) and 10(-5) M, respectively. Vinblastine had little effect on the stimulation of the superoxide anion production by digitonin and NaF throughout the concentration range examined. The mechanism of the interaction of these membrane-perturbing stimulants and vinblastine is discussed. (Author abstract) (24 Refs)

118. OXYGEN TENSION, CELLULAR RESPIRATION, AND REDOX STATE AS VARIABLES INFLUENCING THE CYTOTOXICITY OF THE RADIOSENSITIZER MISONIDAZOLE.

Taylor YC, Rauth AM
(c/o Rauth) Physics Div., Ontario Cancer Inst., 500 Sherbourne St., Toronto M4X 1K9 Ontario, Canada
Radiat Res; 91(1):104-123 1982

The O2 dependence for the cytotoxicity of misonidazole (MIS) was measured using Chinese hamster ovary cells and Chinese hamster lung fibroblasts CCL16-B1 and a respiration-deficient (res-) mutant derived from this line. MIS did not significantly affect O2 utilization rates in intact cells, and hence did not alter initial O2 equilibrium values. MIS caused time-dependent changes in cellular O2 utilization rates, which resulted in increased O2 measured in sol. and a sparing effect on remaining viable cells. Changes in O2 utilization rates apparently do not occur in the absence of appreciable toxicity. Having an inherent block in respiration (res- mutant) did not alter sensitivity to cytotoxic effects of MIS under anoxic conditions, indicating that the toxic effects of MIS on respiration do not appear to play a causal role in toxicity. O2 levels less than 200 ppm produced a 50% reduction in the rate of cell killing. At very low levels diffusion problems raise questions about the exact O2 available in the cell. KCN altered both the aerobic toxicity and the hypoxic cell toxicity of MIS; there is evidence for an electron transport relationship in the latter effect. In contrast, the effects of KCN on the aerobic toxicity of MIS may be completely independent of its inhibitory effect on electron transport enzymes (cytochrome oxidase), since KCN modified the sensitivity of res- mutant and parental cell equally. Calculations showed that O2 levels in vivo must be very low for appreciable toxicity to occur with MIS, but the KCN effects suggest that other factors may also determine degree of reductive drug metabolism and toxicity. (35 Refs)

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DECEMBER, 1982

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ANTITUMOR AGENT EFFICACY IN VIVO

1. SENSITIVITIES OF NEW LINES OF MOUSE MAMMARY CARCINOMA TO VARIOUS CYTOSTATICS.

Galstian DA, Manvelian KR, Ezdanian BA, Demirchoglian IG
V. A. Fanardzhian Inst. Roentgenology and Oncology, Erevan, USSR
Zh Eksp Klin Med; 22(2):114-117 1982

The efficacies of cyclophosphamide (CP: positive control), nornitrogen mustard (norNM), and newly synthesized cytostatic agent L-2 were studied in C3HA mice bearing the transplantable mammary gland carcinomas MGC-1 and MGC-2. The tumors, originating from spontaneous adenocarcinomas, had glandular structures, with small solid regions, cellular layers, marked morphologic anaplasia, spherical or elongated nuclei, and numerous mitoses. The animals started to receive ip injections of the cytostatics (5x, in total therapeutic dose) 24-72 hr after tumor transplantation and were followed-up for 8-10 days. CP, norNM, and L-2 provided inhibitions of MGC-1 of 100%, 73%, and 90%, respectively, and inhibitions of MGC-2 of 73%, 70%, and 100%, respectively. The treatments produced slight enlargements of the spleens. (6 Refs) (In RUS)

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2. TOXICITY OF CISPLATIN AND HYDROXYMALONATODIAMMINE PLATINUM (II) TOWARDS MOUSE BONE MARROW AND B16 MELANOMA IN RELATION TO DNA BINDING IN VIVO.

Pera MF, Sessford D, Roberts JJ
Inst. Cancer Res., Royal Cancer Hosp., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Buckinghamshire HP8 4SP, England
Biochem Pharmacol; 31(13):2273-2278 1982

The antitumor selectivity of cisplatin and hydroxymalonatodiammine platinum II (Pt[OHmal(NH3)2]), a second generation platinum drug, was evaluated in C57Bl/Cbi mice bearing advanced intramuscular B16 melanoma. At maximally tolerated doses, Pt[OHmal(NH3)2] produced greater inhibition of growth of the advanced B16 melanoma than did cisplatin. Comparison of dose-response curves for survival of B16 lung colony-forming cells and bone marrow stem cells treated in vivo indicated that selective killing of B16 cells was achieved with Pt[OHmal(NH3)2], whereas cisplatin was relatively nonselective. The extent of reaction of platinum with DNA at doses producing measurable levels of survival in tumor and marrow in vivo was similar to values previously observed in cultured cells treated with cisplatin in vitro. Studies of the amount of platinum bound to DNA in tumor and marrow following administration of the two drugs revealed that the improved selectivity of Pt[OHmal(NH3)2] was associated with a selective increase in the amount of platinum bound to tumor DNA, relative to cisplatin. In addition, platinum lesions produced in DNA by Pt[OHmal(NH3)2] appeared to be more effective in producing tumor cell killing than those produced by cisplatin. No significant excision of total DNA-bound platinum from tumor was observed up to 48 hr after administration of either drug. (Author abstract) (16 Refs)

3. ANTITUMOR EFFECT OF 3-[(4-AMINO-2-METHYL-5-PYRIMIDINYL)METHYL]-1-(2 CHLOROETHYL)-1-NITROSOUREA (ACNU) ON HUMAN COLON CARCINOMAS TRANSPLANTED INTO NUDE MICE.

Kubota T, Hanatani Y, Tsuyuki K, Nakada M, Asanuma F, Okazaki M, Ishibiki K, Abe O, Nakajima E, Maruyama K
Dept. Surgery, Kitasato Inst. Hosp., 9-1, Shirokane 5-chome, Minato-ku, Tokyo 108, Japan
Jpn J Clin Oncol; 12(1):33-41 1982

Effects of 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2 chloroethyl)-1-nitrosourea (ACNU) were studied in two human colon carcinomas (Co-3, well-differentiated adenocarcinoma; and Co-4, poorly-differentiated adenocarcinoma) serially transplanted into the backs of BALB/c male nude mice. Tumor size was measured 3x/wk and treatment, consisting of ACNU (20 and 40 mg/kg body wt) administered iv 1x, was initiated when the tumor wt was estimated to be 100-300 mg. Slight retardation, but no regression, of Co-3 tumor growth was observed after administration of 40 mg/kg of the ACNU. Regression of the Co-4 tumors was observed in mice treated with either 20 or 40 mg/kg. A dose response effect was observed, and Co-4 tumors regressed to almost half the wt of the initial tumors. Histologically, the treated Co-4 tumors showed marked decrease in cell population, swollen destroyed tumor cells, and massive fibrosis around the tumor cells. Microangiograms of both types of tumors revealed hypervascular features similar to human adenocarcinomas of the colon. Whole-body autoradiography using [ethylene-2-14C]-ACNU showed a peak ACNU concentration min 30 after injection in the Co-3 tumor, but the ACNU was retained in the Co-4 tumor up to min 360 after injection. The antitumor effects of the ACNU were thought to be correlated with the concentration of the drug in the tumor. (21 Refs)

4. EFFECT OF FREE AND BOVINE FIBRINOGEN-BOUND METHOTREXATE AND DIBROMOAMINOPTERIN ON THE DISSEMINATION OF SOLID GARDNER LYMPHOSARCOMA.*

Motycka K, Dyr JE, Macakova A, Slavik K
Inst. Hematology and Blood Transfusion, Charles Univ., 128 20 Prague, Czechoslovakia
Neoplasma; 29(2):197-204 1982

Solid Gardner lymphosarcoma transplanted sc to mice of strain C3H/Sumice does not grow solely at the site of inoculation, but disseminates also to remote tissues. An iv administration of fibrinogen-methotrexate derivative or methotrexate (8-15 mg antimetabolite per 1 kg) to mice with an early tumor, reduced the wt of the local tumor, prolonged their survival time and also the posttransplantation period during which the dissemination of malignant cells could not be detected. When the above substances were given to mice with advanced tumors whose dissemination could be reliably established, Methotrexate proved more effective than its fibrinogen derivative. 3.5'-dibromoaminopterin administered alone or bound to fibrinogen (14.6 mg of antifolate per kg) showed no effect both on survival rate and on tumor dissemination. (Author abstract) (18 Refs)

5. ARTERIAL VERSUS INTRAVENOUS INFUSION THERAPY WITH ADRIAMYCIN IN EXPERIMENTAL RENAL RAT SARCOMA.

Tvete S, Christensen J, Gothlin JH
Dept. Diagnostic Radiology, Univ. Bergen Medical Sch., N-5016 Bergen, Norway
Excerpta Med Int Congr Ser; 575:20-22 1982

Effect of local and systemic administration of adriamycin (Adm) 7 mg/kg body wt was tested on transplantable 20-methylcholanthrene-induced sarcoma in the kidney of rats 6 days after tumor implantation. In 67 animals the drug was administered into the renal artery (ia), in 37 iv, and 30/67 animals received an additional iv infusion of angiotensin II (Ang II). All infusions were administered at a constant rate for 12 min. Frome each of the treatment groups, seven or eight animals were sacrificed at day 1, 2, 4, 6, and 8 after treatment and the av tumor vol was calculated for each sample. At day 4 and 6 after treatment the tumor vol of the ia treated animals was significantly less than that of the iv treated, giving a growth delay of 3 days for ia treatment and 2 days for iv treatment. A small but not significant effect had the addition of Ang II. From day 4 after therapy the growth rate in all treatment groups had recovered to exponential growth. At day 8 no significant difference was observed between the various treatment groups. The tumors attained the vol of the untreated control tumors. According to tumor growth and the accumulation of mitosese the effect of Adm on the tumors was significantly greater with ia than with iv treatment. However the effect of a single infusion was transient. (7 Refs)

6. ANTITUMOR ACTIVITY AND HYDROGEN PEROXIDE RELEASE BY MACROPHAGES ELICITED BY TREHALOSE DIESTERS.

Lepoivre M, Tenu JP, Lemaire G, Petit JF
Institut de Biochimie, Batiment 432, Universite de Paris-Sud, 91405 Orsay, France
J Immunol; 129(2):860-866 1982

Trehalose diesters (natural 6,6'-trehalose dimycolate from Mycobacterium tuberculosis or synthetic (a 76 carbon atom analogue)), when suspended in water, given stable and well-defined emulsions. These emulsions, injected ip in mice significantly limit the growth of P815 syngeneic mastocytoma cells. They elicit macrophages with a cytostatic activity against P815 cells in vitro, strong enough to be expressed at low effector to target ratios (E/T = 1.4) or after a short coincubation period (2 hr). The antitumor potential of these macrophages seems to coincide with their ability to release H2O2 upon pharmacologic triggering. Depressed levels of alkaline phosphodiesterase and beta-galactosidase are proposed as other biochemical markers of cytostatic macrophages. (Author abstract) (44 Refs)

7. HETEROTRANSPLANTATION OF HUMAN MALIGNANT UROGENITAL TUMORS. (3) BASIC STUDIES OF TRANSPLANTABLE HUMAN PROSTATIC CARCINOMA IN NUDE MICE AND SUSCEPTIBILITY TESTING OF SEVERAL PLATINUM COMPOUNDS.

Akimoto M, Tsuboi N, Kawamura N, Nakajima H, Yui Y, Yoshida K, Nishimura T, Tomita M, Kawai H
Dept. Urology, Nippon Medical Sch., Tokyo, Japan
Nippon Hinyokika Gakkai Zasshi; 73(2):143-154 1982

A strain of human prostatic cancer (Pro-1) was serially transplanted in BALB/c-nu/nu mice for 13 generations. The viability of the Pro-1 was almost 100%, and no changes were observed in the state of the tumor cell proliferation. The strain had no hormone receptors, had low susceptibility to diethylstilbestrol diphosphate, and was thought to have little hormone dependency. Platinum compounds were administered ip to the nude mice on days 1, 5, or 9 after transplantation of the tumor. Based on tumor proliferation curves, the tumors were not more susceptible to the anticancer agents 1 wk after administration of the drugs than at the time of the initial administration. The sensitivity of the tumors to cis-diamminedichloroplatinum (CDDP) did not change from generation 17 to 29. Effective doses of the platinum compounds were as follows: CDDP was effective at 5, 2.5, and 1.25 mg/kg; l-Pt(glucuronate)(trans-l-dach) at 25 and 12.5 mg/kg; d-Pt(glucuronate)(trans-d-dach) at 50 and 25 mg/kg; Pt-Br2 (trans-l-dach) was not effective; and l-Pt(oxalate)(trans-l-dach) at 20 mg/kg. The CDDP was the most effective platinum compound and had the safest therapeutic range. Pathohistological changes and tumor proliferation curves were closely related. (29 Refs) (In JPN)

8. DUNNING R-3327H TUMOR RESPONSE TO MULTI-MODALITY THERAPY (MEETING ABSTRACT).

Lakey WH, McPhee MS, Chapman JD, Elliott FG, Ritchie BA, Mador DR, Moore RB, Meeker BE
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

The Dunning R-3327H rat prostatic tumor is an excellent tumor model for the study of human prostatic carcinoma. The biological characteristics of this tumor closely resemble the human counterpart. The purpose of this study was to document the therapeutic response and relapse phenomena of this hormone sensitive tumor to hormone therapy, chemotherapy, radiotherapy and the investigational drug Misonidazole. Prior to treatment all Copenhagen-Fischer F1 hybrid rats had been injected with 2 mm3 core of R-3327H tumor. Tumors were treated after reaching 200 mm3, and then measured weekly. Diethylstilbestrol 50 ugm/kgm or 100 ugm/kgm had no effect on tumor growth rate. Orchidectomy however, greatly decreased tumor growth and serum testosterone levels. Cis-Platinum (60 mgm/m2 ip) suppressed tumor growth rate and was more effective than Vincristine (6 mgm/m2 ip). Current research is establishing the lethal dose and effectiveness of VP-16, VM-26 and Estracyt. Single dose radiation of 1,500 rads and greater has been effective in suppressing tumor growth for up to six months. The radiated tumor histology shows viable-appearing cells. Pretreatment with the hypoxic cell radiosensitizer Misonidazole 0.5 mgm/gm ip followed by 1,000 rads gave the same growth delay as 2,000 rad without Misonidazole. This indicates that a portion of the R-3327H cells are hypoxic. In conclusion, the biological properties of the Dunning R-3327H rat tumor are similar to human prostatic cancer. (no Refs)

ANTITUMOR AGENT EFFICACY IN VITRO

9. ASSOCIATION OF CELL LETHALITY WITH INCORPORATION OF 5-FLUOROURACIL AND 5-FLUOROURIDINE INTO NUCLEAR RNA IN HUMAN COLON CARCINOMA CELLS IN CULTURE.

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Mol Pharmacol; 21(2):468-473 1982

Cytocidal activity of 5-fluorouracil (5-FU) and 5-fluorouridine (5-FUR) was examined by soft agar cloning and the relation of the effects to nucleic acid synthesis and drug incorporation into nuclear RNA was investigated in a human colon carcinoma cell line (HT-29). After 2 hr of drug exposure, 5-FU was toxic only at 10(-3) M whereas almost a 2-log reduction in colony formation was achieved by 10(-5) M 5-FUR. Following a 2-hr or 24-hr exposure to 5-FU and 5-FUR, RNA and DNA syntheses were inhibited in a concentration-dependent manner. The synthesis of low mol wt (4 S) nuclear RNA was not significantly affected by treatment with either drug. No significant difference with the processing of ribosomal RNA (rRNA) was found by long- and short-term exposure to 5-FU and 5-FUR as assessed by lack of accumulation of rRNA greater than 28 S and by inhibition of formation of 28 S and 18 S rRNA. Measurements of the incorporation of [3H]5-FU and [3H]5-FUR into nuclear RNA by agarose gel electrophoresis indicated that 28 S and 18 S rRNA, as well as 4 S RNA, were the main RNA species labeled at noncytotoxic concentrations of drug. At cytocidal drug concentrations, 5-to 10-fold more [3H]5-FU or [3H]5-FUR was incorporated into nuclear 4 S RNA than rRNA. Results indicated that the primary determinant of cell lethality in HT-29 cells is the degree of fluoropyrimidine substitution in nuclear RNA and not inhibition of either DNA or RNA synthesis. (31 Refs)

10. STRUCTURE-ACTIVITY STUDIES WITH THE HOMOLOGOUS SERIES CROSSLINKING DIMETHANESULPHONIC ACID ESTERS (MEETING ABSTRACT).

Bedford P, Fox BW
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Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

The ability of members of the homologous series of dimethanesulphonic acid esters (1-9) to crosslink the DNA of cells derived from the transplantable rodent Yoshida Lymphosarcoma was assayed by the technique of alkaline elution described elsewhere. A peak of interstrand crosslinking occurred after treatment of the cells with hexane dimethanesulphonate (6) which decreased with shorter, or longer alkylating chain lengths. The peak of crosslinking activity by the six-carbon chain member was paralleled by its opitmal cytotoxicity towards the Yoshida cells in culture. Ethylene dimethanesulphonate (2) produced no detectable interstrand crosslinks which was reflected in a lack of in vitro cytotoxicity and in vivo antitumor activity. A possible relationship between DNA-DNA interstrand crosslinking ability and cytotoxicity throughout the series was obtained, which partially but not wholly reflected in the antitumor effectiveness of members of the series. Preliminary data suggest however that the action on hemopoietic and spermatogenic systems may not correlate with DNA-DNA interstrand crosslinking in the same way. (1 Ref)

11. COMPARISON OF 8-AZAADENOSINE (8-AZAADO) AND ITS DEAMINATION PRODUCT, 8-AZAINOSINE (8-AZAINO), AS ANTICANCER AGENTS (MEETING ABSTRACT).

Crabtree GW, Dexter DL, Spremulli EN, Campbell DE, Chu SH, Quevedo WC, Calabresi P, Parks RE
Division of Biology and Medicine, Brown University, Providence, RI, 02912
Proc Am Assoc Cancer Res; 23:848 1982

It is known that 8-AzaAdo has significant activity against cultured human colon cancer cells, and this activity is potentiated when deamination of 8-azaAdo is prevented by 2'-deoxycoformycin. 8-AzaIno, the deamination product of 8-azaAdo, has antitumor activity similar to that of 8-azaAdo against human epidermoid carcinoma and murine adenocarcinoma cells in vitro. Since the antitumor effects of 8-azaAdo alone may be due, in part, to its conversion to 8-azaIno, these two compounds were compared as antitumor agents and for analog nucleotide formation. With the human colon cancer cell lines DLD-1, DLD-1 clone A, DLD-1 clone D and HCT-15 in vitro, both agents are about equitoxic; for 8-azaAdo, ID50 values are 1.6, 1.3, 0.9 and 1.3 uM, respectively, and for 8-azaIno, ID50 values are 2.3, 2.6, 1.3 and 2.5 uM, respectively. When DLD-1 clone A cells are incubated in vitro for 2 hr with either agent at 100 uM, the formation of analog nucleotides, as determined by anion-exchange high performance liquid chromatography, is approximately equivalent in each case. Both agents give large peaks in the triphosphate nucleotide region of chromatograms that have retention times identical to that of 8-azaATP. No peaks were seen with retention times of 8-azaGTP (guanosine triphosphate). Since both 8-azaAdo and 8-azaIno are equitoxic to human colon tumor cells and form similar amounts of analog nucleotides in these cells, this suggests that both agents may act through similar mechanisms. (2 Refs)

12. COMPARISON OF THE EFFECTS OF DIHYDROXYANTHRAQUINONE AND ADRIAMYCIN ON THE SURVIVAL OF CULTURED CHINESE HAMSTER CELLS.

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Cancer Res; 42(9):3631-3636 1982

Dihydroxyanthraquinone [1,4-dihydroxy-5, 8-bis *2-* [*(2-hydroxyethyl)amino*]*ethyl* amino -9,10 anthracenedione (DHAQ) (NSC 279836)] is currently being tested as a cancer chemotherapeutic agent because of its structural similarity to Adriamycin (ADR) and other DNA-intercalating antibiotics. We have therefore studied the effect of DHAQ on the survival of cultured Chinese hamster cells in direct comparison to ADR. Both DHAQ and ADR produced cytotoxicity that was dependent upon the concentration and duration of drug exposure. For 1-hr pulse exposures of asynchronous populations of exponentially growing cells, a 5-to 10-fold greater concentration of ADR than of DHAQ was required to produce the same level of cell killing. There were also differences in the cell cycle age specificity demonstrated by treating at various times before or after selection of cells in mitosis. DHAQ produced the greatest cytotoxicity in cells treated while in G1 or G2; ADR was more effective on cells located in S phase or mitosis. Overall, DHAQ was found to be similar to ADR and other DNA-intercalating antibiotics with regard to the induction of cell lethality. The only differences were those of the concentration required to produce a certain level of effect and of the cell cycle phase specificities for maximum effect. (Author abstract) (34 Refs)

13. INCORPORATION OF THE ANTITUMOR ALKALOID THALIBLASTINE IN LIPOSOMES ENHANCES ITS CYTOTOXIC ACTIVITY IN VITRO.

Todorov DK, Deliconstantinos G
Dept. Physiology, Univ. Athens Medical Sch., Athens 609, Greece
Experientia; 38(7):857-859 1982

The incorporation of the antitumor alkaloid thaliblastine in liposomes greatly enhances its cytotoxicity in Walker S and TLX-5 cell cultures. (Author abstract) (24 Refs)

14. STUDIES ON VARIOUS PARAMETERS INFLUENCING LEUKEMIC CELLS DESTRUCTION BY ALKYL-LYSOPHOSPHOLIPIDS.

Andreesen R, Modolell M, Oepke GH, Common H, Lohr GW, Munder PG
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Anticancer Res; 2(1/2):95-100 1982

Direct cytotoxicity of alkyl-lysophospholipids (ALP) was studied and parameters necessary for the induction of leukemic cell destruction were evaluated. The effect of different serum concentrations on the cytotoxicity of 1-octadecyl-2-methyl-glycero-3-phosphocholine (ET-18-OCH3) on human leukemic cells was studied. Variations in the serum concentration influenced the effect of a constant amount of ET-18OCH3 on the proliferation of tumor cells. In the presence of 40% fetal calf serum, human leukemic cells were only slightly affected. When natural 2-lysophosphatidylcholine was added in increasing amounts to cultures at a constant serum concentration of 10%, the addition resulted in a similar decrease and retardation of ET-18-OCH3 induced cell destruction as was observed with the increasing serum concentration. The addition of 1-octadecyl-glycero-3-phosphocholine (ET-18-OH) also antagonized the destructive effect of ET-18-OCH3. Temperature and pH of the culture medium had a strong influence on leukemic cell destruction. A strong decrease in cell destruction was observed after a temperature decrease of 2 C (37-35 C), while a 2 C increase (37-39 C) resulted in a marked potentiation of cell destruction. When vincristine and ALP, in concentrations which have no toxic effect, were added simultaneously to the cultures, a complete leukemic cell destruction was observed. Inhibition of ALP cytotoxicity was observed when cells were precultured with sterols for 24 hr or when sterols and ALP were added simultaneously to the cultures. Addition of sterols after ALP induced cell destruction exhibited no effect. (30 Refs)

15. PARTIAL CIRCUMVENTION OF RESISTANCE TO 6-MERCAPTOPURINE BY ACYLATED P1,P2-BIS(6-MERCAPTOPURINE-9-BETA-D-RIBOFURANOSIDE-5') PYROPHOSPHATE DERIVATIVES.

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Cancer Res; 42(9):3769-3775 1982

P1,P2-Bis(6-mercaptopurine-9-beta-D-ribofuranoside-5') pyrophosphate [trivial name, bis(thioinosinate) (bis(MPRP))] and its butyryl and hexanoyl derivatives [P1-,P2-bis(O2',O3'-diacyl-6-mercaptopurine-9-beta-D ribofuranoside-5') pyrophosphate] were synthesized by established procedures. The inhibitory effects of bis(MPRP) on cell proliferation in cultures of D98, Chinese hamster lung, L1210 cells, and thiopurine-resistant sublines were determined. Bis(MPRP) exhibited greater activity than did 6-mercaptopurine against resistant D98 cells but was approx equivalent to 6-mercaptopurine or 6-mercaptopurine riboside (MPR) with all other lines. Extracellular degradation of bis(MPRP) by L1210 cells was monitored by high-performance liquid chromatography. The compound was cleaved slowly to MPR and MPR diphosphate in contrast to the rapid extracellular dephosphorylation of MPR monophosphate. Acylated bis(MPRP) derivatives were developed on the basis that bis(nucleotide) compounds capable of entering cells and releasing nucleoside diphosphates might conceivably overcome ribosyltransferase and increase in alkaline phosphohydrolase activities. Unlike bis(MPRP), P1,P2,bis(O2', O3'-dibutyryl-6-mercaptopurine-9-beta-D-ribofuranoside 5') pyrophosphate and P1,P2-bis(O2',O3'-dihexanoyl-6-mercaptopurine-9-beta-D ribofuranoside-5') pyrophosphate were less inhibitory than MPR towards parent L1210 cells but were far more active than the riboside against an MPR-resistant subline. The culture growth-inhibitory activity of the acylated derivatives was considerably greater than could possibly be accounted for by the release of the carboxylic acids. Therefore, it is suggested that partial circumvention of thiopurine resistance may have resulted from cellular uptake of intact acylated bis(MPRP) molecules. (Author abstract) (24 Refs)

16. IN VITRO RESPONSES OF NUDE MOUSE-XENOGRAFTED HUMAN COLON CARCINOMAS EXPOSED TO DOXORUBICIN DERIVATES IN TISSUE CULTURE AND IN THE MOUSE.

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Cancer Res; 42(9):3793-3797 1982

In vitro responses of four xenografted human colon tumors (T183, T219, T245, and T348) to various doses of 1'-deoxydoxorubicin have been investigated. The individual tumors showed marked differences in drug responsiveness, ranging from high sensitivity at low doses (T219; 125 ng/ml) to very low sensitivity at high doses (T245; 4,000 ng/ml). The sensitivity ranking deduced from these in vitro experiments correlates well with the ranking deduced earlier from in vivo drug treatments of transplants of these tumors in the nude mouse. The effect of in vitro drug treatment (4'-deoxydoxorubicin; 250 ng/ml; 1-hr incubation) on the in vivo growth of one of the tumors, T219, in nude mice was investigated. Growth of the tumor in nude mice was markedly delayed by pretreatments in vitro with 4'-deoxydoxorubicin. Furthermore, in vitro responsiveness of the T219 tumor was investigated following in vivo and in vitro treatment of the tumor with 4'-deoxydoxorubicin. Both of the pretreatments produced very similar decreases in drug responsiveness to all of the doxorubicin derivatives tested 4'-deoxydoxorubicin, 4'-O-methyldoxorubicin, 4'-epidoxorubicin, 4'-demethoxydoxorubicin, and N-trifluoroacetylodoxorubicin-14-valeriate. (Author abstract) (12 Refs)

17. EFFECTS OF THE ANTICOAGULANTS, SODIUM WARFARIN AND SODIUM HEPARIN, ON RAT C6 GLIOMA CELLS IN VITRO.

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Diss Abstr Int [B]; 42(6):2327-B 1982

The rat C6 glioma cell line was selected as a model to test cytotoxic effects of the anticoagulants, sodium warfarin and sodium heparin, on brain tumor cells in vitro. Treatment of the cells with sodium warfarin during seven day growth experiments caused a dose-dependent inhibition of cell growth with decreased cellular adherence to the culture plates. Only at the highest dose, 10-2M, was cell viability diminished. Sodium heparin, even at doses as high as 630 units/plate, showed no inhibition of cell growth or cellular adherence and no decrease in cell viability. No changes in cellular protein levels were observed after treatment with 10-3M warfarin or 63 units of heparin. Three hour treatment with 10-3M warfarin yielded no biologically significant changes in 3H-thymidine and 14C-leucine uptake levels or incorporation into DNA or proteins, respectively. Twenty-four hour warfarin treatment caused a significant decrease in 3H-thymidine incorporation into DNA and a significant decrease in 14C-leucine incorporation into protein, when compared to control cells. Treatment of cells with 63 units of heparin did not have any effects on 3H-thymidine uptake or incorporation into DNA after 3 hour or 24 hour heparin incubations. Heparin also did not alter the synthesis of protein. Colony formation studies of interactions between the anticoagulant and selected anticancer agents gave the following results. Heparin is additive with busulfan, 5-fluorouracil, methotrexate, and vincristine. Heparin has a greater than additive effect with BCNU (carmustine), VM-26, and chlorambucil. Warfarin is less than additive with vincristine and VM-26. Warfarin is additive with 5-fluorouracil and busulfan, and warfarin has more than additive effects with BCNU, chlorambucil, and methotrexate. These results suggest that the anticoagulants deserve further study as possible adjuncts to glioma chemotherapy. (no Refs)

POTENTIATION AND SENSITIVITY STUDIES OF ANTITUMOR AGENTS

18. IN VITRO SENSITIVITY OF NITROSOUREA-INDUCED NEUROGENIC TUMORS TO ACNU.

Kida Y, Cravioto H, Hochwald G, Ransohoff J
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Anticancer Res; 2(1/2):79-87 1982

The in vitro sensitivity of three different nitrosourea-induced rat brain tumor cell lines, T9, TR-481, and EB-679, to various concentrations and exposure times of 1-[4-amino-2-methyl-5-pyrimidinyl]methyl-[2 chloroethyl]-3-nitrosourea hydrochloride (ACNU) was studied. The doubling time for TR-481 was 23.3 hr, T9 21.8 hr, and EB-679 28.6 hr. A marked response of T9 cells to 5.0 ug/ml ACNU was observed when the culture medium was not changed. In concentrations greater than 5.0

ug/ml, the cell number began to decrease on the second day and the process was irreversible. Exposures of TR-481 to ACNU resulted in a dose-dependent dissociation of the growth curve, with a moderate to severe suppression of growth. EB-679 cell cultures grew as rapidly as those of control cultures despite an exposure to a concentration of 20 ug/ml ACNU. The effects of limited exposure time to ACNU were examined in T9 and TR-481 tumor only. At a concentration of 10 ug/ml ACNU, T9 cells showed a marked dissociation of the growth curves which was apparent with exposure times at 30 and 60 min. Despite a clearly dose-dependent cell growth curve in dose-related response, TR-481 cells showed only minor responses to limited exposure times at 10 ug/ml ACNU. The effect on TR-481 following 3-hr exposure approximated that of dose-related response when the ACNU concentration was 40 ug/ml. (44 Refs)

19. EFFECTS OF X-RAYS AND CYCLOPHOSPHAMIDE ON SOLID TUMOURS AND METASTASES IN MICE (MEETING ABSTRACT).

Fowler JF, Chu AM
Gray Laboratory of the Cancer Research Campaign, Northwood, Middlesex, England
Br J Cancer; 45(4):634 1982

Combinations of single doses of localized x-rays and single ip doses of cyclophosphamide (CTX) were tested in mice bearing solid transplanted fibrosarcomas which metastasized spontaneously. The end-points examined were growth delay and local control of the 'primary' tumor, the incidence of distant metastases, and the proportion of mice cured, ie surviving to 120 days with no evidence of disease, primary or metastatic. Growth delay and local control varied more rapidly with x-ray dose than CTX dose, as might be expected for a local agent compared with a systemic drug. However, the incidence of metastases and the overall survival time of the mice also depended more on local dose of x-rays than on CTX dose. This result was unexpected, and shows that, in this tumor system, metastases were eliminated more certainly if the primary tumor was controlled locally. A significant proportion of mice (greater than 50%), was cured of both the primary tumor and distant metastases, only when the highest doses of x-rays and CTX were given simultaneously. Intervals between the 2 agents gave inferior results, intervals of 8 days giving significantly worse results than 4 days. It was better to give the x-rays first in the schedules where any such difference was seen. (no Refs)

20. COMBINATION DRUG STUDIES: NITROIMIDAZOLE POTENTIATION OF MELPHALAN ACTIVITY IN VIVO (MEETING ABSTRACT).

Sheldon PW, Batten E
Physics Division, Institute of Cancer Research, Sutton, Surrey, England
Br J Cancer; 45(4):632 1982

Our studies have shown that many nitroimidazole compounds potentiate the activity of melphalan against the anaplastic MT tumor in WHT mice. The potentiation increased with increasing octanol-water partition coefficient and electron affinity of the compounds. The mechanism of this potentiation remains uncertain. However, metastatic and post-irradiation studies indicate that melphalan does penetrate to, and is active against, the hypoxic tumor cell population. Further, the presence of these hypoxic cells is a prerequisite for the potentiation of melphalan activity. However, the expression of this potentiation probably occurs, not in hypoxic cells, but in the oxic-cell population. Our studies have shown that the potentiation is not due to nitro-imidazole-induced hypothermia, elimination of the recovery of melphalan-induced potentially lethal damage, nor solely to a pharmacological response. (no Refs)

21. DO NITROIMIDAZOLES INCREASE THE THERAPEUTIC INDICES OF CYTOTOXIC AGENTS IN VIVO? (MEETING ABSTRACT).

Workman P, Twentyman PR
MRC Clinical Oncology and Radiotherapeutics Unit, Hills Road, Cambridge, England
Br J Cancer; 45(4):631 1982

We have investigated the effects of nitroimidazoles and other agents on the in vivo activity of several cytotoxics. Regrowth-delay assays were used for the RIF-1 and KHT sarcomas in C3H mice, and clonogenic survival in RIF-1. Lethality and WBC count were the normal-tissue and end-points. In neither tumor was melphalan activity improved by 2-5 mmol/kg MISO (misonidazole) (similar results were obtained for the EMT6 tumor in BALB/c mice). Likewise, little enhancement occurred with cyclophosphamide (CTX). At 5 mmol/kg MISO dose-modification factors approx 2 were obtained with low CTX doses in RIF-1, but this fell to 1.3-1.4 at higher CTX doses. Also, with 1.65 mmol/kg MISO the LD50 for CTX was reduced by 1.2-1.3. Tumor response to 7.5 mg/kg chlorambucil (CHL) was enhanced by 2.5 mmol/kg MISO (DMFs approx 2), but similar DMFs were found for normal tissues, indicating no therapeutic gain. KHT response to CCNU (lomustine) was improved by 2.5 mmol/kg MISO, particularly at lower doses, though the DMF was less than 2. For clonogenic survival in RIF-1 the DMF was 1.3-1.4. Since LD50 was reduced by 1.2 and the WBC count not at all, a therapeutic gain is indicated. With both CHL and CCNU, greater enhancement than for MISO was obtained with several lipophilic nitroimidazoles, particularly benznidazole (Ro 07-1051). Also, the non-electron-affinic agents SKF 525A and imidazole were more effective than MISO with CHL. For CCNU this was true of SKF 525A, but imidazole was ineffective. Normal-tissue experiments with these combinations are in progress. (no Refs)

22. ENHANCEMENT OF CCNU CYTOTOXICITY BY MISONIDAZOLE: POSSIBLE THERAPEUTIC GAIN.

Hirst DG, Brown JM, Hazlehurst JL
Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Br J Cancer; 46(1):109-116 1982

Enhancement of CCNU (lomustine) cytotoxicity by misonidazole (MISO) was studied in three tumors and two normal tissues in the mouse. The three experimental tumors (SCCVII/St, EMT6 and KHT) showed very different sensitivities to CCNU alone, but MISO enhanced the cell killing in each case. The effect was not always dose-modifying, so that the CCNU dose range for the greatest enhancement was different in each of the tumors. In all three tumors, enhancement increased with dose of MISO. The effect on two normal tissues, marrow (CFU-S) and testis (spermatogonia), was also investigated. Enhancement of marrow toxicity could be demonstrated only at CCNU doses greater than 12.5 mg/kg, so that at lower CCNU doses there was a therapeutic gain equal to the tumor enhancement ratio. The spermatogonia effect, however, showed enhancement by MISO similar to that seen in the tumors at all CCNU doses up to 20 mg/kg. (Author abstract) (20 Refs)

23. FAILURE OF SHORT-TERM TREATMENT WITH FLURBIPROFEN TO ENHANCE THE THERAPEUTIC EFFECT OF CYCLOPHOSPHAMIDE AGAINST RODENT SARCOMAS AND A LEUKAEMIA.

Heckford SE, Eccles SA, Powles TJ, Alexander P
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Br J Cancer; 46(1):51-57 1982

Animals bearing metastatic fibrosarcomas were treated with cyclophosphamide (CY) alone or in combination with flurbiprofen (FP), an inhibitor of prostaglandin synthesis. FP did not affect local growth of fibrosarcomas, and the incidence of distant metastases after resection of the 'primary' implants was comparable in treated and control groups. Treatment with CY retarded growth of the fibrosarcomas and reduced the proportion of animals which succumbed to metastases, but this was not altered significantly by additional treatment with FP. FP did not affect the survival of rats bearing a lymphoid leukemia. The lifespan of animals treated with CY was increased significantly, but the concomitant administration of FP did not enhance this effect. (Author abstract) (26 Refs)

24. TENIPOSIDE (VM-26)- AND ETOPOSIDE (VP-16-213)-INDUCED AUGMENTATION OF METHOTREXATE TRANSPORT AND POLYGLUTAMYLATION IN EHRLICH ASCITES TUMOR CELLS IN VITRO.

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Cancer Res; 42(9):3648-3653 1982

Teniposide (VM-26) and etoposide (VP-16-213) were evaluated for their effects on methotrexate transport and metabolism in Ehrlich ascites tumor cells in vitro. VM-26 (10 uM) does not alter influx of methotrexate but slows efflux of the drug which leads to an increase in the steady-state level of exchangeable antifolate. VM-26 stimulation of net methotrexate transport occurs within 5 min of exposure of cells to VM-26 concentrations of from 10 to 50 uM; removal of extracellular VM-26 results in a rapid and complete reversal of this effect. As extracellular VM-26 is raised to 50 uM, the progressive rise is net methotrexate uptake observed is due not only to elevated exchangeable antifolate but to an enlarged nonexchangeable pool of intracellular drug as well, a major portion of which is methotrexate polyglutamyl derivatives. VM-26 does not alter the intracellular water or the chloride distribution ratio. Glucose partially reverses the stimulatory effect of VM-26 but to a lesser extent than glucose reversal of the vincristine-induced stimulation of net methotrexate transport. VP-16-213 also stimulates net methotrexate transport in a manner qualitatively similar to that of VM-26. However, 100 uM VP-16-213 is required to yield the same quantitative stimulation as seen for 10 uM VM-26. VP-16-213-induced augmentation of intracellular methotrexate polyglutamate levels is also demonstrated. These results indicate that VM-26 and VP-16-213 enhance net cell accumulation of methotrexate and methotrexate polyglutamyl derivatives in the Ehrlich ascites tumor in vitro at concentrations of these agents which are achieved in vivo. Potential therapeutic synergism between methotrexate and epipodophyllotoxins on this basis is therefore possible and is currently under evaluation in animal tumor systems. (Author abstract) (36 Refs)

25. POTENTIATION OF THE ANTIMITOCHONDRIAL AND ANTIPROLIFERATIVE EFFECTS OF BIS(GUANYLHYDRAZONES) BY PHENETHYLBIGUANIDE.

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Cancer Res; 42(9):3592-3595 1982

The ability of methylglyoxal-bis(guanylhydrazone) (MGBG) and 4,4'-diacetyldiphenylurea-bis(guanylhydrazone) to interact with the hypoglycemic agent, phenethylbisguanide (DBI), in affecting the bioenergetic functions of isolated rat liver mitochondria was studied. DBI was found to increase markedly the inhibitory effect of either 4,4'-diacetyldiphenylurea-bis(guanylhydrazone) or MGBG on respiration of isolated rat liver mitochondria. Conversely, these bis(guanylhydrazones) enhanced the inhibitory potency of DBI and increased the apparent affinity of mitochondria for the drug. As with MGBG and 4,4'-diacetyldiphenylurea-bis(guanylhydrazone), the potassium cationophore, valinomycin, increased the sensitivity of mitochondrial respiration to DBI. It is suggested that the enhancement of bis(guanylhydrazone) inhibition of mitochondrial respiration by DBI involves inhibition of proton fluxes across the inner mitochondrial membrane and the subsequent alkalinization of the mitochondrial matrix. This drug interaction was extended to the level of antiproliferative activity in which DBI was found to potentiate the growth-inhibitory effect of MGBG on murine L1210 leukemia in vivo. (Author abstract) (37 Refs)

26. MODULATION OF 1-BETA-D-ARABINOFURANOSYLCYTOSINE METABOLISM AND CYTOTOXICITY IN L1210 CELLS BY FLUOROPYRIMIDINE PRETREATMENT.

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Cancer Res; 42(9):3550-3556 1982

The effect of pretreatment with the fluoropyrimidines 5-fluorouracil (FUra), 5-fluorouridine (FUrd), 5-fluoro-2'-deoxyuridine (FdUrd), and 5'-deoxy-5-fluorouridine (5'dUrd) on the intracellular metabolism and in vitro cytotoxicty of 1-beta-D-arabinofuranosylcytosine (ara-C) was explored in L1210 cells. A 4-hr exposure to 100 uM FUra, FUrd, or FdUrd produced greater than 3-fold increments in the intracellular accumulation of [3H]deoxyctidine, and 2-fold increments in the intracellular accumulation of [3H]ara-C were produced over a 1-hr exposure. Intracellular 1-beta-D-arabinofuranosylcytosine 5'-triphosphate levels in cells exposed to these three agents were also increased over 2-fold. L1210 cells exposed sequentially to 1 uM FUra, FUrd, or FdUrd followed by 5 uM ara-C for 1 hr resulted in synergistic cell killing measured by soft-agar cloning. Although intracellular 2'-deoxycytidine 5'-triphosphate levels were reduced in cells treated for 4 hr with FUra and FUrd, this was not associated directly with the maximum accumulation of ara-C. FdUrd treatment was as effective as FUra and FUrd at enhancing ara-C accumulation and 1-beta-D-arabinofuranosylcytosine 5'-triphosphate formation and producing synergistic cytotoxicity; however, the 2'-deoxycytidine 5'-triphosphate pools were minimally affected. 5'-Deoxy-5-fluorouridine did not increase intracellular ara-C accumulation, reduce-intracellular 2'-deoxycytidine 5'-triphosphate levels, or enhance ara-C cytotoxicity. This sequential drug interaction is similar to that which we have observed when methotrexate precedes ara-C and provides a rational basis from which further in vivo studies can be designed. (Author abstract) (36 Refs)

27. THE EFFECT OF MISONIDAZOLE ON THE CYTOTOXICITY AND DNA CROSS-LINKING ACTIVITY OF AN ACTIVATED SULFIDOCYCLOPHOSPHAMIDE IN HYPOXIC MOUSE LEUKEMIA CELLS.

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Mol Pharmacol; 22(1):175-181 1982

Synergistic toxicity of misonidazole (MISO) and 4-S-(propionic acid)-sulfidocyclophosphamide (C-2) was demonstrated by measurements of colony-forming ability of hypoxic mouse L1210 leukemia cells, and the effect of MISO on DNA cross-linking capabilities of C-2 were studied. At various concentrations of C-2, cell kill of hypoxic L1210 cells from 2.5 milli(m)M MISO was enhanced in relation to C-2 concentration. With concentrations of MISO from 2.5 to 20 mM with 10 uM C-2 the toxicity of C-2 was enhanced by increasing MISO levels. Alkaline elution profiles were used to assess the degree of interstrand cross-linking occurring in L1210 DNA following exposure to 300 rads x-rays in the presence of 10 uM C-2, 2.5 mM MISO, or the combined drugs at these concentrations. MISO alone produced few if any DNA single-strand breaks, whereas C-2 and C-2 + MISO caused cross-linking, with a greater frequency for the combination of two agents than for C-2 only. Cross-linking was highest approx 6 hr after exposure, with almost complete removal of cross-links in DNA by 15 hr. The enhancement of C-2 toxicity by MISO yields effects beyond the additive effects alone. The fact that cross-linking effects of C-2 were not immediate in the presence of MISO suggests that enhanced transport of C-2 is not the mechanism of potentiation; rather it seems to be an effect on the action at the DNA target, which may be the mechanism in potentiation of other chemotherapeutic drugs by MISO. (30 Refs)

28. POTENTIATION OF INDICINE N-OXIDE CYTOTOXICITY BY FE (III) COMPLEXES (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:807 1982

The effects of Fe (III) complexes and FeCl3 on the cytotoxicity of pyrrolizidine alkaloid N-oxides was studied. Fe(III)-EDTA and Fe(III)-DETAPAC (20 mg/kg x 9 days) were inactive when given alone but significantly increased the survival of leukemia P-388 tumored mice receiving a nonactive dose of indicine N-oxide (200 mg/kg x 9 days), by 60% and 100% respectively. FeCl3 (20 mg/kg x 9 days), given with this dose of indicine N-oxide produced no significant increase in survival. Fe(III)-EDTA also increased the survival observed with a higher active dose of indicine N-oxide (400 mg/kg x 9 days) from 81% to 106%. Fe[illegible]-EDTA appeared to reduce increased survival seen with indicine (400 mg/kg x 9 days) from 62% to 25%. Fe(III)-EDTA (1 mM), which alone had no effect on the growth of Chinese hamster ovary (CHO) cells in vitro, produced up to a three-fold decrease in the concentration of indicine N-oxide required to inhibit CHO cell growth by 50% (IC50). Indicine N-oxide and indicine alone exhibited similar IC50s. Fe(III)-EDTA produced a much smaller decrease in IC50 for indicine. DMSO (0.5%) had no effect on the increased toxicity of indicine N-oxide observed in the presence of Fe(III)-EDTA. This finding fails to support a hydroxyl radical mediated cytotoxic effect for indicine N-oxide. (no Refs)

29. CHEMOTHERAPEUTIC RESPONSE IN TRANSPLANTED MURINE BLADDER CANCER (MEETING ABSTRACT).

Babayan RK, Hong WK, Carpinito GA, Krane RJ
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

The FANFT-induced poorly differentiated transitional cell carcinoma of the bladder in C3H mice (MBT-2, Soloway) has served as an excellent animal model for the screening of chemotherapeutic agents. In an attempt to reproduce the results achieved by others and look for improved effectiveness of therapy, a number of single agents and combinations of agents were tested in the flank nodule model. Mice underwent subcutaneous flank implantation of 0.06-0.08g of tumor from syngeneic donors. At day 7 with palpable nodules present, animals were randomized into groups of 15. Chemotherapeutic testing was begun using cis-platinum (DDP) (3 mg/kg), epipodophyllotoxin (VP-16) (30 mg/kg), Vindesine (Vin)(0.5 mg/kg) and methotrexate (MTX) (30 mg/kg) as single agents. Chemotherapy was administered intraperitoneally twice weekly. Effectiveness of therapy was determined by twice weekly measurement of tumor size in 3 perpendicular diameters with vernier calipers. Tumor volume was estimated by D1 x D2 x D3/2. Statistically significant growth retardation as compared to untreated controls was achieved with DDP and VP-16. Combination chemotherapy with VP-16 and DDP showed a growth retardation exceeding the results achieved by either agent alone. (no Refs)

30. HUMAN GLIOMAS - IN VITRO CHEMOSENSITIVITY TESTING BY GROWTH ASSAY (MEETING ABSTRACT).

Byrne TN, Shapiro JR, Yung WK, Shapiro WR
No affiliation given
Neurology; 38(4,part2):A155 1982

An in vitro assay was designed to predict the chemosensitivity of gliomas in vivo and test new drug protocols. Equal numbers of cells are plated in monolayer culture. After 48 hours, cells are incubated with multiple drug concentrations for 1 hour, washed, and reincubated until controls show confluent growth. The cells are trypsinized and counted. The final cell number at each drug concentration is plotted as a percentage of control. The resulting curve is a function of the initial surviving fraction of heterogeneous cells and their relative growth rates. The area under the curve is a sensitivity index; the smaller the area, the more sensitive the cell line. Using BCNU (carmustine) at 1,5,10, and 15 ug per milliliter, the areas for three cell lines were 319, 859, and 1076. Because growth assays measure both cell kill and reversible cell damage, they demonstrate drug effect at lower concentrations than does the colony forming assay (CFA). Thus, the dose that produced 50% growth inhibition (ED50) for one clone was 2.2 ug per milliliter BCNU, whereas the comparable ED50 using CFA was 7.5 ug per milliliter. The assay can measure chemosensitivity of the heterogeneous populations found in tumor biopsies and may help select chemotherapeutic agents. (no Refs)

TOXICITY AND SIDE EFFECTS OF ANTITUMOR AGENTS

31. TOXICITY OF POLYALKYLCYANOACRYLATE NANOPARTICLES II: DOXORUBICIN-LOADED NANOPARTICLES.

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J Pharm Sci; 71(7):790-792 1982

The possibility of significantly reducing toxicity of an anticancer drug such as doxorubicin by fixing it on polyisobutylcyanoacrylate nanoparticles was studied. It was shown that, when the drug was adsorbed on nanoparticles, significant reduction of both mortality and wt loss of mice were recorded under various administration schedules. Furthermore, cardiotoxicity was decreased due to the poor uptake by the myocardium. (Author abstract) (7 Refs)

32. DIFFERENTIAL PROTECTION AGAINST ALKYLATING AGENT INJURY IN TUMOR AND NORMAL TISSUES (MEETING ABSTRACT).

Phillips TL, Yuhas JM
No affiliation given
First Conference on Radioprotectors and Anticarcinogens, June 21-24, 1982, Washington, DC. National Bureau of Standards 41 pp., 1982.

In our laboratory we have carried out a series of experiments investigating the effect of WR-2721 on the response of intestinal crypt cells, bone marrow CFUs cells, and the EMT6 mouse mammary carcinoma. Using the maximally tolerated dose of adriamycin, bleomycin, BCNU (carmustine), cis-platinum, cyclophosphamide, 5-fluorouracil, L-phenylalanine mustard, methotrexate and nitrogen mustard, the response of CFUs (colony-forming units) crypt cells and tumor were evaluated. Not all drugs were used in each tissue because in some cases no response to particular agents were observed in one of the three tissues. Chemoprotection of the bone marrow CFUs at 50% survival level ranged from a high of a DMF of 10 for cyclophosphamide to a low of 1.0 for 5-fluorouracil. All of the alkylating agents were protected against, as was adriamycin, to a certain extent in the CFU assay. Using the intestinal crypt cell assay, dose modifying factors (DMF) of 1.3 were seen for adriamycin and BCNU at a survival of 10 crypts, whereas the DMF was 1.8 for cis-platinum and 2.0 for melphalan and nitrogen mustard. No protection was seen against 5-fluorouracil and methotrexate damage. Protection against the effect of cytotoxic agents on the regrowth of the EMT6 tumor was absent for all of the alkylating agents tested, including nitrogen mustard, BCNU, cyclophosphamide, and cis-platinum. There was also no protection against the cell kill induced in the tumor by 5-fluorouracil. (no Refs)

33. COMPARISON OF THE EFFECTS OF DIHYDROXYANTHRAQUINONE (DHAQ, NSC 279836) AND ADRIAMYCIN ON THE ENHANCEMENT OF RADIATION-INDUCED TOXICITY IN RATS (MEETING ABSTRACT).

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Twenty-fourth Annual Meeting of the American Society of Therapeutic Radiologists, October 25-29, 1982, Orlando, Florida American Society of Therapeutic Radiologists; 1982

DHAQ is a recently synthesized compound that is being investigated as a possible cancer chemotherapeutic agent because of its structural similarity to Adriamycin (ADR). Like ADR, DHAQ is reported to produce cardiomyopathy that appears to be dependent upon the cumulative dose received. We have compared the effects of DHAQ to those of ADR, both agents being administered to rats ip at doses of 2.5, 5.0, or 10.0 mg/kg body weight. A single injection of 2.5 mg/kg ADR had no effect on animal survival, 100% being alive at 120 days after treatment. A dose of 5.0 mg/kg ADR resulted in 47% survival at 120 days after treatment; 10.0 mg/kg killed all animals by day 50, with a median survival time of 34 days. Single injections of DHAQ at 2.5 and 5.0 mg/kg produced 53 and 40% survival at day 120, respectively. The dose of 10.0 mg/kg DHAQ killed all animals by day 57, with a median survival time of 8 days. When the 5.0 mg/kg ADR treatment was combined with 15 Gy thoracic irradiation using 25 MV x-rays (a dose that reduced survival at 120 days to 73%), only 20% of the animals survived to day 120. Analysis shows that ADR and thoracic irradiation interacted in at least an additive manner. On the other hand, when 5.0 mg/kg DHAQ was combined with 15 Gy thoracic irradiation there was no increase in animal deaths to day 120, 43% surviving the combination compared to 40% after DHAQ alone. Treatment with DHAQ alone or in combination with 15 Gy was equivalent to a radiation dose of approximately 17.5 Gy based on the linear cumulative lethality model. The patterns of interaction of thoracic irradiation plus high doses (5.0 mg/kg) of DHAQ and ADR are in contrast to our previous findings that the short-term lethalities induced by low doses (1.0 mg/kg) of DHAQ and ADR were and were not enhanced, respectively, by the addition of thoracic irradiation. These results indicate that, although the target for ADR-induced lethality in rats may well be the heart (based on the interaction with thoracic irradiation), the target for DHAQ-induced immediate toxicity does not appear to be located in the thorax. Efforts are continuing to identify histologically the critical organs affected by DHAQ that result in acute toxicity. (no Refs)

34. TERATOGENIC ACTION OF PLATINUM THYMINE BLUE.

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Life Sci; 31(8):757-762 1982

The teratogenic activity of the antitumor agent cisplatinum-2-thymine (platinum thymine blue) was investigated in rats. Pregnant Wistar-derived albino rats were given single ip injections of an aqueous soln of platinum thymine blue (PTB) at 1 day of pregnancy from Day 5 through Day 14 (sperm day = Day 0). The dosages used ranged from 20 to 80 mg/kg maternal body weight. At autopsy (Day 20) fetuses were recovered and subsequently examined for skeletal and soft-tissue abnormalities. PTB was embryolethal and teratogenic at several stages during rat gestation. Embryonic death occurred following all doses, and was dose dependent, except at Day 5. The majority of malformed fetuses, however, were observed only after treatment at Day 6 or 7 following injection with 50, 60, or 80 mg/kg. Eye defects were the predominant abnormality followed by hydrocephalus, gastroschisis, and ectopia cordis. The skeleton was only slightly affected. PTB is a potent inhibitor of DNA synthesis, but its mechanism of teratogenic action is unknown. (Author abstract) (21 Refs)

35. HEMATOPOIETIC PRECURSOR CELLS IN MICE TREATED WITH 4-DEMETHOXYDAUNORUBICIN AND DOXORUBICIN.

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JNCI; 68(6):971-976 1982

The hematologic toxicity of 4-demethoxydaunorubicin (4-dmDNR), a new anthracycline more potent and less cardiotoxic than doxorubicin (Dx), was studied. Dose-survival curves of bone marrow hematopoietic precursor cells (HPC) in situ were determined with the use of (C57BL x C3H)F1 mice and with assays of colony-forming units (spleen, culture, and erythroid) by in vivo and in vitro methods. Time response of HPC was followed in mice treated at days 0, 2, and 5 with 0.75 mg 4-dmDNR/kg or 4.5 mg Dx/kg and in mice receiving 2.23 mg 4-dmDNR/kg or 3.96 mg Dx/kg twice a wk for 4 wk. The dose-survival curves of HPC for 4-dmDNR were exponential. Slight differences in sensitivity among assayed populations were seen. Although the doses of 4-dmDNR required to reduce the survival of HPC to 37% were similar or lower than those of Dx, following intermittent treatment with doses of 4-dmDNR with the same optimal antitumor activity as the Dx, 4-dmDNR seemed to have a lesser effect on hematopoietic progenitors and a greater effect on peripheral blood cells than did Dx. However, during prolonged administration 4-dmDNR appeared to be toxic at every hematopoietic level. (Author abstract) (22 Refs)

36. MODIFICATION OF CYTOTOXIC DRUG EFFECTS BY THE SULPHYDRYL COMPOUND WR 2721 (MEETING ABSTRACT).

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Br J Cancer; 45(4):632 1982

There is evidence that the sulphydryl compound WR 2721 is able to provide greater protection of normal tissues than tumors against both ionizing radiation and a number of cytotoxic drugs. We have studied the ability of this compound to protect C3H/He mice against the toxicity of cyclophosphamide (CTX), CCNU (lomustine), cis-platinum (CIS-Pt) and chlorambucil (CHL), and also its effect upon the therapeutic response to these agents of the RIF-1 and KHT sarcomas. At a dose of 400 mg/kg of WR 2721, the acute LD50 of CTX was reduced by a factor of approx 1.3. At a lower dose of 200 mg/kg, similar protection against CTX was seen, but little if any change in the acute LD50s of the other 3 agents. There was also no evidence of protection by 200 mg/kg of WR 2721 against WBC depression on Day 3 after CTX, CCNU or CIS-Pt. For both tumors, the response to CTX was also reduced by 400 mg/kg of WR 2721, and to a similar extent in terms of LD50. At 200 mg/kg, however, little if any reduction in tumor response was seen; hence differential protection of some normal tissues may result. In this series of experiments, tumors were grown im in the hind limb. Experiments are in progress to assess whether tumor protection by WR 2721 may be site-dependent through differences in tumor vascularity. (1 Ref)

37. RESIDUAL INJURY TO THE HEMOPOIETIC MICROENVIRONMENT FOLLOWING SEQUENTIAL RADIATION AND ALKYLATING AGENTS.

Wathen LM
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Diss Abstr Int [B]; 42(7):2730-B 1982

To assess the hemopoietic impact following combined modality therapy, mice received four weekly intraperitoneal doses of cyclophosphamide, 160 mg/kg (CY) one week after 1500 rad leg irradiation (LI). This treatment inhibited repopulation of endogenous nucleated cells to less than 60% of normal at 1, 2, 4, and 6 months postirradiation. Differential marrow counts revealed that 1500 rad LI + CY suppressed erythroblasts, myeloid, and lymphoid cells more than either modality alone. To directly assess the damage of sequential 1500 rad LI and CY on the microenvironment, marrow stromal cells were flushed from the femoral marrow and cultured as adherent cell colonies. They were suppressed to less than 30% normal for 3 months following combined modality treatment. Hemopoietic stem cells (CFU-S) and granulocyte-macrophage precursors (CFU-C) were supressed but exhibited different patterns of partial recovery. To determine whether busfulfan, an alkylating agent known to produce aplastic anemia, would cause microenvironmental damage similar to that seen following cyclophosphamide, mice received four weekly intraperitoneal doses of busulfan, 20 mg/kg (BU) one week after 1500 rad leg irradiation (LI). In general, the pattern of hemopoietic suppression following sequential radiation and busulfan was similar to that following sequential radiation and cyclophosphamide. However, at 4 and 6 months post-irradiation, the busulfan treated mice had a more severe suppression of CFU-S, CFU-C, and marrow stromal cells than mice treated with cyclophosphamide alone. In addition, an excessive number of myeloid blast cells and a severe erythroid depletion suggested that the BU-treated mice were preleukemic. (no Refs)

38. THE DESIGN, SYNTHESIS, IN VITRO AND IN VIVO TESTING OF NOVEL AMINOACYL AND MACROMOLECULAR P-HYDROXYPHENYLHYDRAZIDES AS IMINOQUINONE PRO-DRUGS.

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Diss Abstr Int [B]; 42(7):2787-B 1982

The proposed iminoquinone precursor, alpha-N-(carboxymethyl)-p-hydroxyphenylhydrazine (CHP) was covalently linked to five different L-amino acids (AA)-leucine, phenylalanine, alanine, glutamate and lysine--to give five AA-CHP dipeptide analogs. Furthermore, tertbutoxycarbonyl-1-leucyl-CHP (Boc-Leu-CHP) was covalently linked to bovine serum albumin (BSA) resulting in the synthesis of Boc-Leu-CHP-BSA and Leu-CHPBSA macromolecular pro-drugs (MPDs). In vivo toxicity experiments with DBA/2J mice using free CHP-OEt, five AA-CHPs, and two MPDs showed that the LD50, onset of death, and histologic manifestations of organ toxicity (or lack thereof) depended greatly on the moiety to which CHP was bound. If cysteine was given one hour prior to and two or three hours after an LD100 dose of Leu-CHP or Phe-CHP as administered, a dramatic increase in the survival of the treated mice obtained. In vivo treatment experiments using five AA-CHPs and two MPDs in DBA/2J mice bearing L1210 leukemia failed to demonstrate any inhibition of tumor progression or prolongation of survival of the treated animals. In the case of Leu-CHP-BSA, at non-toxic doses an unexpected shortening of the life span of treated animals relative to the controls was found. (no Refs)

39. INTRAVENOUS LETHALITY STUDY IN CDF1 MICE AND TOXICITY STUDY IN BEAGLE DOGS OF DIHYDRO-5-AZACYTIDINE HYDROCHLORIDE (NSC-264880) TASK I.

Chin AE, Stromberg PC, Whalen JE
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Intravenous Lethality Study in CDF1 Mice and Toxicity Study in Beagle Dogs of Dihydro-5-Azacytidine Hydrochloride (NSC-264880) Task I. Available from National Technical Information Service, Springfield, VA, as PB82-195751:, 207 pp., 1981.

Studies of the toxicity of the antineoplastic agent, dihydro-5-azacytidine hydrochloride (NSC-264880), were conducted in the mouse and dog in order to define the dose:lethality relationship in the mouse and the toxic effects in both species. In these studies dihydro-5-azacytidine was administered intravenously using a single and five consecutive daily dose schedule to male and female CDF(1) mice and Beagle dogs. The calculated mouse LD90, LD50, and LD10 in the single dose lethality study were 3,340.6 (10,021.8), 2,559.1 (7,677.3), 1,960.5 (5,881.5) mg/kg (mg sq m) respectively in males and 3,227.9 (9,683.7), 2,564.6 (7,693.8), 2,037.6 (6,112.8) mg/kg (mg/sq m) respectively in females. In the five consecutive daily dose study the mouse LD90, LD50, and LD10 values were determined to be 1,705.1 (5,115.3), 1,411.7 (4,235.1), 1,168.8 (3,506.4) mg/kg (mg/sq m) respectively in males, and 1,221.6 (3,664.8), 886.9 (2,660.7), 643.9 (1,931.7) mg/kg (mg/sq m) respectively in females. Toxicity studies of dihydro-5-azacytidine in mice were conducted using the calculated mouse LD50, LD10, and 1/2 LD(10) for each sex and the same dosage schedules used in the mouse lethality studies. To assess the toxicity of dihydro-5-azacytidine in the Beagle dog, doses for dogs equivalent to the mouse final combined (male and female) 2x LD10, LD10, and 1/10 LD(10) (12,000; 6,000; 600 mg/sq m respectively) for the single dose regimen, and the mouse final combined LD10, 1/2 LD(10). (Author abstract)

40. STUDIES ON THE ABILITY OF THYMIDINE TO MODIFY THE CHEMOTHERAPEUTIC ACTIVITY AND METABOLISM OF 5-FLUOROURACIL AND 1-BETA-D-ARABINOFURANOSYLCYTOSINE IN RATS AND MICE.

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Diss Abstr Int [B]; 42(9):3647-B 1982

The therapeutic efficacy of equitoxic doses of concurrent thymidine (TdR) and 5-fluorouracil (FU) vs FU alone was studied in rats and mice bearing transplantable colon tumors. Under the conditions employed, TdR did not significantly alter the antitumor activity of FU in rats or mice. The toxicity of FU, however, could be enhanced in vivo by co-administration of TdR. Analysis of rat plasma showed increased circulating levels of TdR and thymine (T) and reduced levels of deoxycytidine (CdR) during TdR infusion. TdR effects on FU metabolism included: (1) TdR infusion reduced systemic FU catabolism and increased circulating levels of FU relative to FU alone; (2) TdR did not alter the incorporation of FU into tumor RNA, but appeared to enhance FU incorporation into the RNA of normal tissues; (3) tumor 5-fluorodeoxyuridylate (FdUMP) levels were reduced by TdR; however, thymidylate synthetase inhibition by FdUMP was complete using FU or FU and TdR. Because TdR infusion reduced rat plasma CdR levels, the effect of TdR on 1-beta-D-arabinofuranosylcytosine (ara-C) activity in rats was examined. TdR enhanced ara-C toxicity, the magnitude depending upon the treatment schedule. The best tumor growth inhibition resulted from infusion of TdR prior to ara-C. Whereas TdR increased ara-C triphosphatase (ara-CTP) levels over control in both tumor and host tissues, 3-6 hrs post-TdR, ara-C levels were elevated only in the tumor. Consequently, the toxicity but not the antitumor activity of ara-C could be reduced by delayed infusion of ara-C following TdR. These data provide evidence for in vivo modulation of a metabolite, CdR (presumably an index of intracellular CdR metabolism), by another metabolite, TdR, resulting in augmentation of the effects of an antimetabolite, ara-C. (no Refs)

41. INHIBITION OF HUMAN MOTOR ENDPLATE CHOLINESTERASE BY ALKYLATING ANTINEOPLASTIC AGENTS (MEETING ABSTRACT).

Namba T, Fujii M, Harada H, Grob D
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Fed Proc; 41(3):1721 1982

Antineoplastic agents caused prolonged apnea when succinylcholine was used as muscle relaxant. The apnea is due to inhibiton of acetylcholinesterase (AChE) of the motor endplate, but the effect of antineoplastic agents has been studied only in plasma pseudocholinesterase (PChE), which has no known physiologic role. Human motor endplate AChE was obtained as isolated muscle membrane, and it was inhibited by alkylating agents, mechlorethamine (pI50-3.12), dacarabazine (2.23), cyclophosphamide (1.67), and ifosfamide (1.49). There was no substantial inhibition or there was interference of AChE measurement by alkylating agents, carmustine, streptozocin, and thiotepa; antimetabolites, cytarabine, fluorouracil, methotrexate and tegafur; and natural products, doxorubicin, mitomycin, vinblastine and vincristine. Human plasma PChE was inhibited by cyclophosphamide (pI 50-3.26), mechlorethamine (3.22), thiotepa (2.32), dacarbazine (1.79), ifosfamide (1.66) and carmustine (1.57), and not significantly by other agents. Mechlorethamine and ifosfamide inhibited motor endplate AChE and plasma PChE practically equally, while dacarbazine was a more selective inhibitor of motor endplate AChE. Inhibition of human motor endplate and red blood cell AChE was practically identical, and therefore red cells would be a preferable sample to plasma in monitoring cholinesterase inhibition by antineoplastic agents. (no Refs)

42. ANTHRACYCLINE ANTICANCER DRUG-STIMULATION OF NADPH-DEPENDENT, REACTIVE OXYGEN-MEDIATED LIPID PEROXIDATION IN MOUSE HEART AND LIVER MICROSOMES (MEETING ABSTRACT).

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National Cancer Institutes, National Institutes of Health, Bethesda, MD, 20205
Fed Proc; 41(3):1575 1982

Several adriamycin-like anthracycline drugs with redox capability stimulated NADPH dependent lipid peroxidation (LP) monitored by malonaldehyde formation as much as 10-fold in mouse heart or liver microsomes, without the addition of exogenous iron salts, when incubated with a NADPH-generating system under an oxygen atmosphere. Adriamycin, daunorubicin, desacetyladriamycin and aclacinomycin A all maximally stimulated LP in the concentration range of 100 to 200 uM, whereas carcinomycin and 4-demethoxydaunorubicin produced equivalent stimulation at 25 to 30 uM and at higher concentrations were inhibitory. Mitomycin C (500 uM) markedly stimulated LP in heart microsomes, but interestingly, had little effect in liver microsomes. In contrast, 5-Iminodaunorubicin (10 uM) potently inhibited both heart and liver microsomal LP. Superoxide dismutase, reduced glutathione, 1,3-dimethylurea or EDTA significantly diminished anthracycline-stimulated heart and liver microsomal LP, suggesting a role for superoxide, hydroxyl radical and possibly endogenous iron in these reactions. In addition, adriamycin, and several other drugs stimulated LP in lung and kidney microsomes suggesting that drug-mediated reactive oxygen generation may have toxic consequences in those organs as well as in heart and liver. (no Refs)

43. PROTECTIVE ROLE OF THIOLS IN CYCLOPHOSPHAMIDE-INDUCED UROTOXICITY AND DEPRESSION OF HEPATIC DRUG METABOLISM.

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(c/o Gurtoo) Dept. Experimental Therapeutics, Roswell Park Memorial Inst., New York Dept. Health, Buffalo, NY, 14263
Cancer Res; 42(9):3688-3695 1982

One of the serious toxicities of cyclophosphamide chemotherapy is urotoxicity. In addition to causing leukopenia, high-dose cyclophosphamide caused both depression of hepatic microsomal enzyme activities and extensive urinary bladder damage, suggesting that a common biochemical mechanism may be responsible for both of these effects. Administration of 180 or 200 mg cyclophosphamide per kg to Wistar rats caused 41 to 67% decrease in aryl hydrocarbon hydroxylase activity, a 21 to 54% decrease in aminopyrine demethylase activity, and a 34 to 40% decrease in cytochrome P-450 content. This dose of cyclophosphamide also caused hematuria as well as necrosis and edema in the urinary bladder. Administration of N-acetylcysteine or sodium-2-mercaptoethane sulfonate (mesnum) with cyclophosphamide, while not protecting against leukopenia, protected against the enzymatic inactivation and urotoxicity. The biochemical basis of these observations is discussed. The results suggest that a common metabolite of cyclophosphamide, most probably acrolein, is responsible for both of these undesirable effects of cyclophosphamide therapy. Use of combinations including cyclophosphamide and an appropriate thiol may increase the therapeutic index of this drug. (Author abstract) (35 Refs)

44. PROTECTION AGAINST ACUTE DAUNORUBICIN TOXICITY BY ICRF-187 AND RELATED COMPOUNDS (MEETING ABSTRACT).

Herman E, El-Hage A, Witiak D
Ohio State University, Columbus, OH
Fed Proc; 41(3):1477 1982

The acute toxicity induced by the antineoplastic agent daunorubicin (D) can be attenuated by pretreatment with ICRF-187, (+) 1,2-bis-(3,5-dioxopiperazinyl-1-yl) propane. The mechanism for this action is not completely understood. To better define this activity, optimal pretreatment times, dosages and structural requirements were studied. D (25 mg/kg, iv) given to Syrian golden hamsters resulted in weight loss, severe GI (gastrointestinal) toxicity and 100% mortality within 3 weeks. Pretreatment with ICRF-187 1 hr before D attenuated GI toxicity; 60% of the animals survived greater than or equal to 8 weeks. Smaller ICRF-187 doses (12.5-50.0 mg/kg) also increased survival, but body weights of these animals were 10-30% below control after 5 weeks. ICRF-187 (100 mg/kg) pretreatment times were varied; 48 hr pretreatment enhanced survival (45%) but no protection occurred if the compound was given greater than or equal to 12 hr after D. Survival was maximal when ICRF-187 was given from 3 hr before to 3 hr after D. Hamsters were pretreated with 15 ICRF-187 analogues (6.25-200.0 mg/kg each). Limited protection was noted with only 3 analogues. At the highest tested dose (200 mg/kg) of ICRF-192 (central chain ethyl), ICRF-197 (central cyclobutane) or ICRF-200 (N-methyl substitution on ring imide function), survival at 8 weeks was 30-38%. Results indicate that ICRF-187 remains the most active compound; future studies of its GI activity should provide insight into the mechanism of protection against D toxicity. (no Refs)

45. REVERSIBLE PYRIDOXINE DEPLETION AS A MECHANISM FOR MISONIDAZOLE NEUROTOXICITY (MEETING ABSTRACT).

Eifel PJ, Brown DM, Lee WW, Brown JM
Department of Radiology, Stanford Medical School, Stanford, CA, 94305
Twenty-fourth Annual Meeting of the American Society of Therapeutic Radiologists, October 25-29, 1982, Orlando, Florida American Society of Therapeutic Radiologists; 1982

Depletion of pyridoxal (PDL) nutritionally or by drugs can cause a neuropathy and seizures which are completely reversed (or prevented) by administration of adequate doses of pyridoxine (PYR). PDL could be depleted in nerve cells (and elsewhere) following administration of misonidazole (MIS) by binding to the final reduction product of MIS, 2-amino-misonidazole (NH2-MIS), to form a Schiff base. We have prepared NH(2)-MIS and added it to PDL-HCl. Spectrophotometric analysis of the mixture revealed a new peak which was not produced by NH(2)-MIS or PDL alone. This peak reflected an increase in yellow product and is characteristic of Schiff base formation. If MIS neurotoxicity is caused by the occurrence of this reaction in vivo, it should be preventable by administration of pyridoxine at a dose equal to or greater than the amount of NH(2)-MIS being produced. Experiments with three month old female BALB-c mice (21-23 gm) receiving daily (7 d/wk) intraperitoneal (IP) injections of MIS (580 mg/kg) with or without IP injections of PYR (200 mg/kg) revealed markedly diminished toxicity in the PYR treated mice. Time to onset of neurologic signs (ie foot splay), maintenance of body weight and survival were all improved by more than a factor of two with administration of PYR. Simultaneous PYR administration did not alter the pharmacokinetics of MIS either initially or after repeated daily injections, so it would not be expected to alter the radiosensitizing effect of MIS. PYR is a non-toxic drug in humans and can be given in daily amounts much larger than should be required to prevent neurotoxicity. (no Refs)

PHARMACOKINETICS OF ANTITUMOR AGENTS

46. DEGRADATION OF MELPHALAN IN AQUEOUS SOLUTIONS - INFLUENCE OF HUMAN ALBUMIN BINDING.

Ehrsson H, Lonroth U
Karolinska Apoteket, S-104 01 Stockholm, Sweden
J Pharm Sci; 71(7):826-827 1982

The protein binding and degradation rate of melphalan in human albumin solutions and plasma have been investigated. In plasma, melphalan is bound 69.0 +-3.4% (25 C, melphalan concentration 25 ug/ml). The stability of melphalan when bound to albumin is about 3x higher (k = 3.07 x 10(-2) +-0.48 x 10(-2) hr-1) than unbound in solution (k = 1.14 x 10(-1) +-0.01 hr-1). (Author abstract) (5 Refs)

47. CONCENTRATION-DEPENDENT DISAPPEARANCE OF FLUOROURACIL FROM PERITONEAL FLUID IN THE RAT: EXPERIMENTAL OBSERVATIONS AND DISTRIBUTED MODELING.

Collins JM, Dedrick RL, Flessner MF, Guarino AM
Biomedical Engineering and Instrumentation Branch, Div. Res. Services, NCI, NIH, Bethesda, MD, 20205
J Pharm Sci; 71(7):735-738 1982

The rate of disappearance of fluorouracil from peritoneal fluid has been experimentally measured and mathematically modeled. The experimental data were obtained following the installation of 50 ml of dialysis fluid which contained an initial fluorouracil concentration ranging from 24 uM to 12 mM. The rate of disappearance was strongly dependent upon concentration. A distributed model has been formulated which incorporates concepts of diffusion with saturable metabolism and non-saturable capillary uptake in the tissue surrounding the peritoneal fluid. This model successfully describes the experimental observations and also suggests that the effective penetration depth into tissue is highly dependent upon concentration. (Author abstract) (20 Refs)

48. PHARMACOKINETICS OF CYCLOPHOSPHAMIDE AND CYCLOPHOSPHAMIDE METABOLITES IN THE MOUSE AND THEIR INFLUENCE ON THE THERAPEUTIC EFFECT OF 'ACTIVATED' CYCLOPHOSPHAMIDE (4-HYDROXYCYCLOPHOSPHAMIDE).

Voelcker G, Haeglsperger R
Gustav-Embden-Zentrum der Biologischen Chemie, Johann Wolfgang Goethe-Universitat, Theodor-Stern-Kai 7, 6000 Frankfurt/Main 70, W. Germany
Arzneim Forsch; 32(6):639-647 1982

Therapy tests with 2-[bis(2-chloroethyl)amino]tetrahydro(2H)-1,3,2 oxazaphosphorinane-2-oxide (cyclophosphamide (CP)) and its metabolites 4-hydroxycyclophosphamide (4-OH-CP) and phosphoramide mustard (NLDP) were carried out on heterotransplanted human breast cancer in nude mice. The results are: (1) Only 4-hydroxycyclophosphamide can imitate the therapeutic effect of cyclophosphamide. (2) The therapeutic effect is not proportional to the product of concentration and time (c x t) in blood as tumor growth was more inhibited with lower c x t when high concentrations were present over a short time than with higher c x t and adjustment of low concentrations over a long time. Pharmacokinetic measurements in mice demonstrated that this behavior is due to the elimination of 'activated' cyclophosphamide by Michaelis-Menten kinetics (Km = 146 nmol/ml-1, Vmax = 18 nmol/ml-1/min-1) and to the fact that increasing blood concentration of 'activated' cyclophosphamide is accompanied by its increased distribution towards the peripheral compartment as may be seen from the volumes of distribution of the peripheral and central compartments. From blood concentration curves of cyclophosphamide and cyclophosphamide metabolites we calculated that 91% of the cyclophosphamide administered is activated. Eighty-one percent of the 'activated' cyclophosphamide is detoxified to 4-keto-CP and carboxyphosphamide (Carboxyph). Since the detoxifying enzymatic system is more active against aldophosphamide than against 4-hydroxycyclophosphamide the non-detoxified rest of 'activated' cyclophosphamide is composed of 80% of 4-hydroxycyclophosphamide and 20% of aldophosphamide. (Author abstract) (35 Refs) (In GER)

49. CHANGES IN THE PHARMACOKINETICS OF METHOTREXATE BY ENCAPSULATION IN LIPOSOMES AND THE VARYING EFFECT ON EXPERIMENTAL TUMORS.

Freise J, Diehl V

Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, W. Germany

Onkologie; 4(1):4-5 1981

The effects of encapsulation of methotrexate in liposomes on the pharmacokinetics and therapeutic effect of the drug were studied in mice bearing experimental Ehrlich ascites tumors. In comparison with free methotrexate or NaCl control injections, methotrexate in liposomes significantly reduced the number of ascites cells by a factor of 3-4. A review of literature indicates that encapsulation slows excretion of methotrexate and increases the amount of the drug that concentrates in tumor tissues. (6 Refs) (In GER)

50. PHARMACOKINETICS AND METABOLISM OF CYTOSINE ARABINOSIDE IN THE CENTRAL NERVOUS SYSTEM.

Spector R

Dept. Medicine, Univ. Iowa Hospitals, Iowa City, IA, 52242

J Pharmacol Exp Ther; 222(1):1-6 1982

The pharmacokinetics and metabolism of [3H]cytosine arabinoside ([3H]araC) in the CNS of New Zealand white rabbits was studied in vitro and in vivo. Brains were obtained from rabbits immediately after overdosing with pentobarbital and cardiac puncture. The portion of the brain above the left lateral ventricle was sliced in two different directions. Slices of brain tissue and isolated choroid plexuses were incubated separately in artificial cerebrospinal fluid (CSF) containing 5 nanoM [3H]araC. In both tissues the uptake of [3H]araC was saturable. However, after 30 min the tissue/medium (T/M) ratio did not exceed 1.0. In the choroid plexus after 15 min incubation 8 +-2% of the 3H within the plexus was present as [3H]araC phosphates. In the brain slices after 30 min incubations 4 +-1% of the 3H was present as [3H]araC phosphates. To measure the in vivo behavior, [3H]araC was injected into rabbits along with unlabeled cytosine arabinoside (araC: 0, 2, or 20 micromoles). High concentrations of araC in the CSF decreased the clearance of araC from the CSF. Cells in all regions of the brain studied absorbed and phosphorylated araC. Phosphorylation was saturable. However, even in the presence of 20 umoles araC, some araC was phosphorylated to the triphosphate form. (23 Refs)

SCREENING FOR ANTITUMOR AGENTS AND RELATED METHODOLOGY

51. ALLYLIC ESTERS AS POTENTIAL ANTITUMOR AGENTS.

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Diss Abstr Int [B]; 42(6):2387-B 1982

The allylic ester function is one of the structural features required for antitumor activity and toxicity of mitomycins, pyrrolizidine alkaloids, and their analogs. To study potential intramolecular interactions that control the reactivity of allylic esters, Anderson and Dewey made and examined various derivatives of 2,3-bis(hydroxymethyl)-7-exabicyclo[2.2.1]hept-2-ene. Dimethyl 2,3-bis(acetoxymethyl)-7-oxabicyclo[2.2.1]hepta-2,5 diene-5,6-dicarboxylate (I) was the most potent in the leukemia L1210 tissue culture assay. The goal of this investigation was to synthesize analogs of I, in an effort to evaluate the factors which influence the reactivity of the allylic ester. The acetate ester of I was replaced with the carbamate ester which is known to be more stable toward degradation by serum esterase. Dimethyl 2,3-bis(hydroxymethyl)-7-oxabicyclo[2.2.1]hepta-2,5 diene-5,6-dicarboxylate bis(N-butylcarbamate) was active in the mouse P388 leukemia assay (but was not reproducible). The N-methyl analog was the most toxic, and toxicity was found to decrease as lipophilic character increased. All the other compounds tested were found to be inactive. (no Refs)

52. DEVELOPMENT OF IN VITRO CHEMOSENSITIVITY SCREENING FOR THE R3327 MAT-LU PROSTATE-DERIVED TUMOR LINES (MEETING ABSTRACT).

Fleischmann J, Heston WD, Bramlet G, Fair WR
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City Missouri. American Urological Association 254 pp., 1982.

The results of chemotherapy or endocrine manipulation for treatment of advanced cancer of the prostate are poor. There is little data on chemotherapeutic testing in vitro prior to chemotherapy. Using the R3327 MAT-Lu prostate-derived tumor, we have developed a method for in vitro chemosensitivity testing based on a modification of the Human Tumor Stem Cell Assay developed by Salmon, et al. The MAT-Lu tumor cells are maintained in liquid culture as previously described by us, and are then collected for in vitro testing. The in vitro method requires mechanical dispersion on the cells and exposure to the chemotherapeutic agents prior to growth in soft agar. Chemosensitivity is determined as a function of colony growth in drug-treated cells compared to control. Preliminary data indicate the MAT-Lu tumor is resistant to most chemotherapeutic agents. Some growth suppression was achieved with high concentrations of diethylstilbesterol. Combination chemotherapy utilizing pre-treatment of the cells with alpha-difluoromethylornithine and subsequent methylglyoxal-bis (guanylhydrazone) resulted in better growth suppression than any single agent tested. These in vitro results will be correlated with chemotherapeutic trials in animals. (1 Ref)

53. SYNTHESIS OF CEPHALOTAXINE ESTERS AND THEIR ANTITUMOR ACTIVITY.

Li S, Sun H, Lu S, Zhang S, Lu F, Dai J, Xu Y
Shanghai Inst. Materia Medica, Academia Sinica, Shanghai, People's Republic of China
Yaoxue Xuebao; 16(11):821-827 1981

Twelve new cephalotaxine esters were synthesized and their antitumor activities studied on three murine experimental tumors (leukemia 615, brain tumor 22 and Ehrlich ascites tumor). Preliminary results showed that the isopropyl (or isopentyl), the tertiary hydroxyl and the methoxycarbonylmethyl groups of their side chain are essential for their antitumor activity. Synthetic procedures are detailed. (6 Refs) (In CHI)

54. STUDIES ON ANTITUMOR ANTIBIOTIC 1588. III. EXPERIMENTAL TREATMENT OF ANIMAL TUMORS.

Yang G, Xu Z
Inst. Antibiotics Res., Third Pharmaceutical Factory, Shanghai, People's Republic of China
Yaoxue Xuebao; 16(11):811-814 1981

Effects of antibiotic 1588 on experimental tumors were studied and results showed it to be markedly active against murine B22, Lio-1, U-14 and S-180 when given ip (12.5 mg/kg x 10 days), with tumor inhibition rates of 50.6% to 90%. It also prolonged the survival of animals bearing the ascitic forms of Ec, ARS, HCA and Walker-256. When compared with zhengguangmycin and pingyangmycin (bleomycins), the antitumor effects of two of its major components on solid S-180 were slightly higher. (8 Refs) (In CHI)

55. MACROMOLECULAR ACTIVE COMPONENTS IN CHINESE TRADITIONAL HERBAL DRUGS.

Yang M
Sichuan Provincial Inst. Chinese Materia Medica, Sichuan Province, People's Republic of China
Yaoxue Tongbao; 16(11):29-37 1981

Macromolecular components such as polysaccharides, peptides and proteins are widely present in Chinese herbal drugs and were formerly regarded as inert. However, mass screening of plants for anticancer drugs in recent yr have shown that many macromolecules of plants have tumor-inhibiting activities. This review covers the following topics: (1) antitumor polysaccharides, (2) polysaccharides with activities on the cardiovascular system, and (3) antitumor peptides and proteins. (83 Refs) (In CHI)

56. SYNTHESIS AND BIOLOGICAL ACTIVITY OF 5'-SUBSTITUTED 5-FLUOROPYRIMIDINE NUCLEOSIDES.

Ajmera S, Danenberg PV
Dept. Biochemistry, Univ. Southern California, Sch. Medicine, Los Angeles, CA, 90033
J Med Chem; 25(8):999-1002 1982

The compound 5'-deoxy-5-fluorouridine (5'-dFUrd, 1) possesses a significantly higher chemotherapeutic index than other fluoropyrimidines as a result of its being selectivity cleaved in tumors to 5-fluorouracil (FUra) by uridine phosphorylase. Because 1 is a relatively poor substrate for this enzyme, we synthesized a series of 5'-deoxy-5'-substituted-5-fluorouridine (FUrd) derivatives in an effort to obtain compounds that might have improved substrate interactions compared to 1 and thus possibly be better prodrugs of FUra. Three derivatives, 5'-O-tosyl-FUrd (13), 5'-O-mesyl-FUrd (14), and 5'-deoxy-5'-bromo-FUrd (15), had cytostatic activity against L1210 and CCRF-

CEM leukemic cells in culture superior to that of 1. In preliminary in vivo antitumor studies against L1210 leukemic cells in mice, 5'-deoxy-5'-chloro-FUrd (4), 5'-O-mesyl-FUrd (14), and 5'-deoxy-5'-fluoro-FUrd (18) gave percent increases in life span of 64, 58, and 58, respectively, compared to a value of 20 for compound 1. (Author abstract) (18 Refs)

57. SYNTHESIS AND ANTITUMOR ACTIVITY OF NEW PLATINUM COMPLEXES.

Brown DB, Khokhar AR, Hacker MP, Lokys L, Burchenal JH, Newman RA, McCormack JJ, Frost D
Vermont Regional Cancer Center, Univ. Vermont, Burlington, VT
J Med Chem; 25(8):952-956 1982

A new type of antitumor platinum complex has been prepared and examined for antitumor activity against L1210 leukemia both in vitro and in vivo. The coordination environment of platinum in these complexes consists of three anionic chloride ions and a positively charged amine. The positive charge is introduced by monoprotonation or monoalkylation of a diamine. Platinum(IV) derivatives have been prepared for several of the complexes, and a water-soluble sulfate derivative has been prepared for one of them. Several of these complexes exhibit significant in vitro activity, and trichloro(3-aminoquinuclidinium)platinum(II) (QTP) exhibits significant in vivo activity as well. An increase in life span of approx 40% has been observed using QTP. QTP is toxic at doses slightly in excess of effective doses. (Author abstract) (13 Refs)

58. CORRELATION OF ANTITUMOR ACTIVITY AND ELECTRON DEFICIENCY OF NITROFURANYLHYDRAZONE COMPOUNDS.

Newman RA, Strauss MJ, Renfrow R
Vermont Regional Cancer Center, Univ. Vermont, Burlington, VT, 05405
J Pharm Sci; 71(7):831-832 1982

Phenylhydrazone derivatives of 5-nitro-2-furaldehyde were tested for antitumor activity against L-1210 murine leukemia in vitro. A substantial increase in antitumor activity was observed in these series of compounds as the electron deficiency of the six-membered aromatic ring was increased. A possible mechanism of action involving drug reduction as well as antibacterial and antitumor efficacy is discussed. (Author abstract) (19 Refs)

59. PROPERTIES OF HUMAN GLIOMA LINES (MEETING ABSTRACT).

Ponten J
Department of Pathology, University of Uppsala, P. O. Box 553, S-751 22 Uppsala, Sweden
In Vitro; 18(3,part2):319 1982

Twenty-eight lines of glioblastoma multiforme have been established from a consecutive series of biopsies. This represents a success rate of about 15 per cent. The growth control properties have been analyzed with respect to density dependent inhibition of DNA synthesis, multiplication in the presence of normal cells and requirement for growth factors. The lines have been individually distinct with respect to these and a variety of other factors. A new technique - miniclone analysis - has been used to elucidate lack of glioma growth control. The method permits evaluation of several hundred unselected single cell clones in one experiment. All tested glioma lines have lacked the normal inhibitory response caused by a reduced solid support characteristic of non-neoplastic glia. Miniclone analysis was used to assess chemosensitivity of glioma cells with respect to BCNU, (carmustine), ENU (ethylnitrosourea), bleomycin, adriamycin and streptozotocin. This new method permitted us to operationally distinguish cytolytic, cytostatic and cytoretarding effects and to design effective in vitro drug combinations. (no Refs)

60. ANTILEUKEMIC AND CYTOTOXIC CONSTITUENTS OF DIRCA OCCIDENTALIS (MEETING ABSTRACT).

Badawi MM, Handa SS, Kinghorn AD, Cordell GA, Farnsworth NR
Department of Pharmacognosy and Pharmacology, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL, 60612
Twenty-third Annual Meeting of the American Society of Pharmacognosy, August 1-5, 1982, Pittsburg, Pennsylvania American Society of Pharmacognosy; :A76 1982

A chloroform extract of the twigs and flowers of Dirca occidentalis Gray (Thymelaeaceae), collected in California, was found to possess both in vivo and in vitro activity in the P-388 test system. Bioassay-directed fractionation afforded two antileukemic daphnane esters, Pimelea factor P2 and dircin, a new compound. A further four constituents of this species, the three lignans, (-)-medioresionol, (+)-syringaresinol and (-)-lariciresinol, as well as the coumarin, daphnoretin, were found to exhibit cytotoxic activity. (no Refs)

61. ANTITUMOR MACROMOLECULAR SUBSTANCE FROM LITTLENECK CLAM, MERCENARIA MERCENARIA (MEETING ABSTRACT).

Tanaka M, Shimizu Y
Department of Pharmacognosy and Environmental Health Sciences, University of Rhode Island, Kingston, RI, 02881
Twenty-third Annual Meeting of the American Society of Pharmacognosy, August 1-5, 1982, Pittsburg, Pennsylvania American Society of Pharmacognosy; :A70 1982

We reported that some marine invertebrates contains tumor inhibitory substances in their macromolecular fractions. An extract of littleneck clam, M mercenaria, was one of the four promising samples in the investigation. The water extract was fractionated by ultrafiltration, and the fraction of molecular weight larger than 300,000 daltons, which showed a strong antitumor activity against sarcoma 180, was chromatographed on DEAE (diethylaminoethyl)-Sepharose CL-6B. The partially purified antitumor active fractions from DEAE-chromatography showed an inhibitory effect on complement dependent hemolysis in vitro. The activity was higher than the well-known antitumor polysaccharides, zymosan and lentinan. We will discuss a further purification and partial characterization of this antitumor substance. (no Refs)

62. ADDITIONAL NEW MAYTANSINOIDS FROM TREWIA NUDIFLORA: 10-EPITREWIASINE AND NORTREWIASINE (MEETING ABSTRACT).

Powell RG, Smith CR
Northern Regional Research Center, 1815 N. University Street, Peoria, IL, 61604
Twenty-third Annual Meeting of the American Society of Pharmacognosy, August 1-5, 1982, Pittsburg, Pennsylvania American Society of Pharmacognosy; :A67 1982

Previously we have described the isolation and characterization of six new maytansinoids from Trewia nudiflora L (Euphorbiaceae). These compounds, the most abundant of which is trewiasine, have potent tumor-inhibiting properties in experimental systems as well as a variety of insect-control properties. Further work has revealed two additional members of this series--10-epitrewiasine and nortrewiasine. Isolation of these new maytansinoids was achieved by HPLC (high performance liquid chromatography), and structures were elucidated by high-field proton NMR (nuclear magnetic resonance) C-13 NMR, EIMS, and negative ion CIMS. (no Refs)

63. ANTINEOPLASTIC ALKALOIDS OF CONOPHARYNGIA DURISSIMA (MEETING ABSTRACT).

Iwu MM
Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria
Twenty-third Annual Meeting of the American Society of Pharmacognosy, August 1-5, 1982, Pittsburg, Pennsylvania American Society of Pharmacognosy; :A59 1982

Leaves of C durissima yielded antineoplastic bisindoles voacamine, conoduramine, conodurine and 18-decarbomethoxyvoacamine, together with three new compounds conofarinine, isoconofarinine and conofarinidine. The compounds were characterized from their spectral data and chemical reactions. (no Refs)

64. ANTITUMOR FRACTIONATION OF EUPHORBIA LAGASCAE SEEDS USING SIMPLE BIOASSAYS (MEETING ABSTRACT).

Ferrigni NR, Meyer BN, Powell RG, Smith CR, McLaughlin JL
Department of Medicinal Chemistry and Pharmacognosy, Purdue University, West Lafayette, IN, 47907
Twenty-third Annual Meeting of the American Society of Pharmacognosy, August 1-5, 1982, Pittsburgh, Pennsylvania American Society of Pharmacognosy; :A21 1982

Ethanol extracts of the defatted seeds of the title plant were active in the 3PS, 9PS, brine shrimp, and crown gall potato disc bioassays. Fractionation was performed, monitoring with the brine shrimp and potato disc assays. Sucrose, esculetin (6,7-dihydroxycoumarin), and piceatannol (3,4,3,'5'-tetrahydroxystilbene) were isolated. The latter two compounds were weakly active in the 9PS cytotoxicity assay (3.9 and 2.5 mg/ml, respectively), and piceatannol was toxic to brine shrimp (LC50 30 ppm). Additional fractionation and bioassays are in progress. (no Refs)

65. PINOCEMBRIN AND GONIOTHALAMIN, TWO BIOACTIVE COMPONENTS FROM GONIOTHALAMUS GIGANTEUS (ANNONACEAE) (MEETING ABSTRACT).

Ebrahim AA, Ferrigni NR, McCloud TG, Cassady JM, Chang CJ, McLaughlin JL
Department of Medicinal Chemistry and Pharmacognosy, Purdue University, West Lafayette, IN, 47907
Twenty-third Annual Meeting of the American Society of Pharmacognosy, August 1-5, 1982, Pittsburgh, Pennsylvania American Society of Pharmacognosy; :A20 1982

Antitumor fractionation of the title plant produced fractions which were consistently toxic to mice in the 3PS assay. F008 (90% MeOH, toxic at 6.25 mg/kg) showed antitumor activity in the crown gall potato disc assay and was also toxic (LC50 215 ppm) to brine shrimp (less than 1000 ppm is considered 'active'). Column chromatography of F008 on silica gel yielded for zones of brine shrimp activity. From the first zone (LC50 less than 10 ppm), the known compounds, (-)-pinocembrin (5,7-dihydroxyflavanone) and goniothalamin (3-ene-5-styryl-2-pyrone) were isolated and identified; both were toxic to brine shrimp. Additional bioassays and fractionations of the other active zones are in progress. We emphasize the speed and simplicity of employing brine shrimp as a bioactivity monitor during phytochemical fractionation. (no Refs)

66. SENSITIVITY TO 1-(4-AMINO-2-METHYL-5-PYRIMIDINYL)METHYL-3-(2 CHLOROETHYL)-3-NITROSOUREA HYDROCHLORIDE (ACNU) OF GLIOMA CELLS IN VIVO AND IN VITRO.

Yoshida J, Shibuya N, Kobayashi T, Kageyama N
Dept. Neurosurgery, Nagoya Univ. Sch. Medicine, 65, Tsuruma-cho, Show-Ku, Nagoya, Japan
Cancer; 50(3):410-418 1982

A new water-soluble nitrosourea (1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2 chloroethyl)-3-nitrosourea hydrochloride, ACNU) was tested for its antitumor activity against four glioma cell lines. Four factors were studied to determine its antitumor activity: inhibition of cell growth, morphologic observation, analysis of DNA histogram with flow microfluorometry, and sensitivity testing with microtest plate. Growth inhibition in response to ACNU was seen in two cell lines (EA-285, U251-MG), whereas two cell lines (YE2-2, T98) were resistant to ACNU. The results of the present sensitivity test concur with those of other examinations that this test is useful in selecting a drug and determining the effective dose. (Author abstract) (21 Refs)

67. TERRECYCLIC ACID A, A NEW ANTIBIOTIC FROM ASPERGILLUS TERREUS. 1. TAXONOMY, PRODUCTION, AND CHEMICAL AND BIOLOGICAL PROPERTIES.

Nakagawa M, Hirota A, Sakai H, Isogai A
Dept. Agricultural Chemistry, Univ. Osaka Prefecture, Sakai, Osaka 591, Japan
J Antibiot (Tokyo); 35(7):778-782 1982

A new antibiotic, terrecyclic acid A was isolated from the culture filtrate of a new isolate of fungus, identified as Aspergillus terreus. The fermentation yields reached about one gram per liter of the broth. Chemical and biological characterization of the antibiotic revealed that it was a new sesquiterpene having a wide antimicrobial spectrum and antitumor activity. (Author abstract) (5 Refs)

68. ON THE ANTITUMOR ACTIVITY OF GALLIUM.

Anghileri LJ, Thouvenot P, Robert J
Lab. Biophysics, Univ. Nancy, 18, Rue Lionnois, F-54000 Nancy, France
Arch Geschwulstforsch; 52(6):479-480 1982

The C3HBA mammary adenocarcinoma was implanted sc into C3H/HeJ mice and 1 wk later animals were given a daily dose of 10 mg gallium chloride per kg body wt in the drinking water for 30 days or until death. Comparison of tumor growth and survival of treated animals did not reveal any statistically significant differences from control mice. Thus, po gallium chloride exhibits no antitumor activity under the conditions of this study. (7 Refs)

69. CC-1065 (NSC 298223), A MOST POTENT ANTITUMOR AGENT: KINETICS OF INHIBITION OF GROWTH, DNA SYNTHESIS, AND CELL SURVIVAL.

Bhuyan BK, Newell KA, Crampton SL, Von Hoff DD
The Upjohn Co., Kalamazoo, MI, 49001
Cancer Res; 42(9):3532-3537 1982

CC-1065 (NSC 2928223) is the most cytotoxic agent tested against cells in culture in our laboratory. The 50% lethal doses for exponentially growing B16 melanoma and Chinese hamster ovary cells were 0.44 and 0.14 ng/ml, respectively, as compared to 35 and 500 ng/ml for Adriamycin. In the human tumor-cloning assay, 1-hr exposure to CC-1065 (0.1 ng/ml) caused greater than or equal to 50% lethality in a broad spectrum of tumors. The dose-survival curves for B16 and Chinese hamster ovary cells were characterized by an initial shoulder followed by an exponential decline with increasing dose. CC-1065 was more lethal to exponentially growing B16 cells (50% lethal dose = 0.44 ng/ml) than to plateau-phase cells (50% lethal dose = 1.2 ng/ml). CC-1065 inhibited DNA synthesis much more than did RNA or protein synthesis. After a 2-hr incubation with drug, inhibition of DNA synthesis was low immediately (0 hr) after drug exposure and reached maximum inhibition about 20 hr later. The doses for 50% inhibition of growth (0.18 ng/ml), survival (0.44 ng/ml), and DNA synthesis (0.15 ng/ml) were in the same range, whereas RNA synthesis was inhibited 50% at a much higher dose (5 ng/ml). (Author abstract) (12 Refs)

STUDIES OF ANTIMETASTATIC AGENTS

70. METASTATIC THYMOMA WITH MYASTHENIA GRAVIS. COMPLETE REMISSION WITH COMBINATION CHEMOTHERAPY.

Butler WM, Diehl LF, Taylor HG, Weltz MD
Univ. South Carolina, Sch. Medicine, Richland Memorial Hosp., 3301 Harden St., Columbia, SC, 29203
Cancer; 50(3):419-422 1982

A 29-yr-old male developed myasthenia gravis 29 months after resection of a 'benign' mediastinal thymoma. Metastatic thymoma was found in the pleura 45 months after the initial surgical resection. Combination chemotherapy with cyclophosphamide and doxorubicin produced a complete remission of the metastatic thymoma which has continued for 13 months. Concurrently, there has been a marked increase in neuromuscular function. (Author abstract) (17 Refs)

71. ARTERIAL INFUSION CHEMOTHERAPY FOR HEPATIC METASTASES (MEETING ABSTRACT).

Pettavel J
No affiliation given
International Symposium on Vascular Perfusion in Cancer Therapy, April 22-23, 1982, Giessen, W. Germany. Klinik fur Allgemeinchirurgie 55 pp., 1982.

Between 1965 and 1982 we infused 158 livers harboring primary or secondary malignancies. We elected arterial infusions (155 cases) to portal infusions (4 cases). Ligation of the proximal hepatic artery with distal infusion of chemotherapy was used in 5 cases. Ligation of a right or left hepatic artery, associated with infusion chemotherapy of the other side, was used 4 times. Major hepatic surgery was combined with artery infusion 7 times. Drugs infused included Fluorouracil (10-18 gm spread over 5-9 days) FUDR (0.25 mg/kg/day), Mitomycin C (10 mg/m2), occasionally, Methotrexate and Adriamycin. Operative mortality was 4.7%. Thirty day cancer mortality was 12%. Gastro-duodenal ulcerations were observed in 8 cases, of which one followed by death. Thrombosis of the infused artery (possibly due to the catheter but more often to the progression of tumor) was a rare but significant complication. Ligation of hepatic artery resulted in tumor necrosis, abcesses and dislodgement of the catheter and was not correlated to longer survivals. Seventy-eight secondary malignancies originating in the colon and rectum have been infused for more than three months. Fifty-five were classified as objective responders (24 complete responses of two months or more, 31 part responses and 17 no change or progression of disease) 6 cases were not evaluated. (no Refs)

72. CONTROL OF METASTASES: NB RAT PROSTATE TUMOR MODEL (MEETING ABSTRACT).

Drago JR, Gallagher C
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

The androgen-insensitive Noble prostate carcinoma tumor model has been used to evaluate various chemotherapeutic agents. This experiment was designed to evaluate the rate of metastatic disease present following therapy with both chemotherapeutic agents as well as antiplatelet medications including acetylsalicyclic acid, heparin, and Indocin. The chemotherapeutic agents used included Cyclophosphamide alone and in combination with Adriamycin. Heretofore the use of Cyclophosphamide in combination or as a single agent has been the most efficacious agent in terms of reducing metastasis and tumor volume control in these Nb rat prostate tumors. In this experiment 60 animals were chosen, 11 in the controls and 10 in the other experimental groups. The control animals had 5 of the 11 with metastases, the acetylsalicyclic acid had 5 of 10 animals with metastases, Indocin and heparin had 0 of 10 animals showing metastases at the time of autopsy. Cyclophosphamide treatment in combination with Adriamycin had a metastatic incidence of 3 of 10 animals, and Cyclophosphamide alone also had a rate of 2 animals with metastatic disease. The control of metastatic disease has been believed to be related to the platelet trapping of tumor cells and it has been postulated that it has been directly or indirectly related to prostaglandin secretion as well. In this experiment the heparin, and anticlotting medication, as well as Indocin, a prostaglandin inhibitor, have resulted in 0 of 10 animals having metastases. This represents only a pilot study and determination of prostaglandin levels in correlation with the various chemotherapeutic modalities is planned for the future as well as repeat of the experiment. However, it is believed that this preliminary data may be of more than passing interest. (no Refs)

73. APPLICATION OF LYMPHANGIOGRAPHY TO DIAGNOSIS AND TREATMENT OF LYMPH NODE METASTASIS.

Hashimoto K
First Dept. Oral Surgery, Tokyo Medical and Dental Coll., Tokyo, Japan
Kokubyo Gakkai Zasshi; 49(1):192 1982

Metastasis-inhibiting and long-term effects of bleomycin (BLM) were studied in Japanese white rabbits given sc transplantation of VX2 experimental tumor cells. Rabbits were divided into five groups as follows: Group I was given no treatment following transplantation, Group II had resections of primary tumor nests 10 days after transplantation, Group III was given intralymphatic injection of lipoidal-BLM (L-BLM; 3 mg/kg) directly after transplantation, Group IV was given direct injection of L-BLM 10 days after transplantation, and Group V was given intralymphatic injection of L-BLM 10 days after transplantation. Group I rabbits died between wk 2-10. Group II rabbits died between wk 5-16. Group III rabbits had a 20-wk survival rate of 4/5. Group IV survival was the same as that of Group I. Group V had a clear prolongation of survival up to wk 5 after injection of the BLM. Histologically, changes were observed in lymph nodes in the early stages after injection of the L-BLM, decreased wk 2-3 after injection, and recovery occurred thereafter. Results showed that direct intralymphatic injection of L-BLM allows direct and prolonged observation of difficult to observe with the aid of lymphangiography of small lymph nodes. This also suggests the possible use of L-BLM for early diagnosis of lymph nodal and localized metastases. (3 Refs) (In JPN)

74. NAFAZATROM (BAY G 6575): INHIBITOR OF TUMOR CELL PROLIFERATION AND METASTASIS (MEETING ABSTRACT).

Honn KV
Wayne State University, Detroit, MI, 48202
Fed Proc; 41(3):333 1982

BAY g 6575 (3-methyl-1-[2-(2-napthyloxy)ethyl]-2-pyrazolin-5-one) is a potent antithrombotic agent which is believed to stimulate vascular wall prostacyclin (PGI2) release. PGI2 is a potent antimetastatic agent. The effects of BAY g 6575 on spontaneous metastasis and tail vein-injected tumor cell metastasis, in addition to tumor cell proliferation (in vitro), were evaluated in the B16 amelanotic melanoma (B16a) and Lewis lung carcinoma (3LL). Daily injection (sc; 0.4-32 mg/Kg) reduced (88-95%) spontaneous tumor cell metastasis to the lung. Pretreatment (3 da, sc:) with BAY g 6575 (3.2 mg/Kg) reduced metastatic tumor colony formation (lung) from iv tail vein injected B16a cells (5 x 10(4)) from the control of 106 to 1.8 colonies. In vitro BAY g 6575 inhibited B16a and 3LL DNA synthesis (3H-thymidine incorporation) over a dose range of 0.1-25 ug/ml (20 to 95% inhibition). Tumor cell proliferation was similarly inhibited in B16a and 3LL. Inhibition (greater than 50%) of subcutaneous tumor growth was observed with BAY g 6575 treatment (3.2 mg/Kg sc daily). These results suggest the use of BAY g 6575 for single agent treatment of tumor growth and metastasis. (no Refs)

75. TREATMENT OF A METASTATIC PROSTATE DERIVED TUMOR WITH SURGERY AND CHEMOTHERAPY (MEETING ABSTRACT).

Kadmon D, Heston WD, Fair WR
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City Missouri. American Urological Association 254 pp., 1982.

We studied the R3327MAT-Lu tumor, a derivative of the Dunning Copenhagen rat prostatic carcinoma, which invariably metastasizes to the lungs following im inoculation in the hind leg. I) Time course of metastases: 64 male rats were inoculated with tumors in their left hind legs, which were then amputated at different time intevals. Twenty-eight days post inoculation the animals were sacrificed. We found that by the 10th post inoculation day, 100% of the animals developed lung metastases. II) Tumor reduction by excision and/or chemotherapy: 77 male rats were inoculated with tumors as above. Tumors were excised on day 10 and/or single dose chemotherapy given on day 14. When sacrificed, 28 days after inoculation, the mean number of lung metastases were: Gr I (control, sham surgery): 512, Gr II (surgery only); 188, Gr III (surgery + ICRF-159 150 mg/Kg): 118, Gr IV (surgery + cyclophosphamide 150 mg/Kg): 57, Gr V (cyclophosphamide 150 mg/Kg + sham surgery): 52, Gr VI (surgery + doxorubicin 10 mg/Kg): 94, Gr VII (doxorubicin 10 mg/Kg + sham surgery): 164. III) Effect of treatment at an early metastatic stage on survival: 44 male rats were inoculated with tumors as above. They were treated as groups I, II, IV and V above. Surgery alone had no effect on survival. Cyclophosphamide alone resulted in no cures, but prolonged survival by a mean of 20 days. The combination therapy group, however, had an overall prolonged survival and a 42% cure rate. (no Refs)

INTERFERON AND OTHER ANTIVIRALS

76. EFFECTS OF HUMAN GAMMA INTERFERON ON CELL GROWTH, REPLICATION OF VIRUS AND INDUCTION OF 2'-5'-OLIGOADENYLATE SYNTHETASE IN THREE HUMAN LYMPHOBLASTOID CELL LINES AND K562 CELLS.

Tomita Y, Cantell K, Kuwata T
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
Int J Cancer; 30(2):161-165 1982

Human alpha interferon (IFN-alpha) and beta interferon (IFN-beta) showed antiviral and anticellular effects on human lymphoblastoid Daudi and P3HR-1 cells, but up to 1,000 units/ml of gamma interferon (IFN-gamma) showed no such effect. Though a fairly high level of dsRNA-dependent 2'-5'-oligoadenylate synthetase (2-5A synthetase) was found in Daudi cells, treatment of these cells with IFN-alpha and beta enhanced the enzyme level in cells at least four-fold, but IFN-gamma did not show any such effect. Lymphoblastoid Raji cells were insensitive to the antiviral and anticellular activities of IFN-alpha, beta and gamma, but 2-5A synthetase was induced in cells by the treatment with IFN-alpha and beta, though the enzyme level was lower than that found in interferon-treated Daudi cells. Human leukemic K562 cells were completely insensitive to IFN-alpha, beta and at the same time to IFN-gamma with regard to the antiviral, anticellular activities and to the induction of 2-5A synthetase. (Author abstract) (31 Refs)

77. GROWTH STATE-SPECIFIC RESPONSIVENESS OF PRIMARY CULTURES OF A NUDE MOUSE-XENOGRAFTED HUMAN COLON CARCINOMA TO 4'-DEOXYDOXORUBICIN AND A CRUDE HUMAN LEUKOCYTE ALPHA-INTERFERON PREPARATION.

van der Bosch J, Zirvi KA
Diabetes Forschungsinstitutr, Auf'm Hennenkamp 65, 4000 Dusseldorf, W. Germany
Cancer Res; 42(9):3789-3792 1982

Improved procedures for the seeding of primary cultures from human colon tumors are described. Responsiveness of primary cultures from human colon carcinoma T348 to a crude preparation of human leukocyte alpha-interferon and a DNA-intercalating experimental anticancer drug, 4'-deoxydoxorubicin, has been investigated. The effect of the interferon preparation on such cultures is shown to be growth state specific; ie, stationary populations are killed, whereas fast-growing cultures are reversibly growth inhibited by the same doses of interferon. In contrast, 4'deoxydoxorubicin kills growing populations, whereas stationary cultures are barely affected by the same concentration of this drug. Interferon antagonizes the cytotoxic effect of 4'deoxydoxorubicin on a growing colon tumor cell population when applied immediately after 4'-deoxydoxorubicin treatment. Implications of this finding for the combined application of several drugs in cancer therapy are discussed. (Author abstract) (11 Refs)

78. INHIBITOR OF SWINE LEUKOCYTIC INTERFERON.

Parfenov VV, Timofeev IV, Zubanova NA
N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Vopr Virusol; (3):338-341 1982

The results of evaluation of the properties of inhibitor isolated from the swine leukocytic interferon (SLI) are reported. The inhibitor showed a heterospecific activity against SLI, human leukocytic interferon, and mouse serum interferon. The inhibitor had a marked antiproliferative effect in the culture of normal human fibroblasts and in the culture of ovarian carcinoma and HeLa cells. (23 Refs) (In RUS)

79. CONTROL OF GROWTH OF A MALIGNANT LYMPHOID CELL LINE BY INTERFERON AND (2'-5') PA (MEETING ABSTRACT).

Leandersson T, Lundgren E, Nordfelth R
Laboratory for Cell and Tissue Culture Research, University of Umea, S-901 85 Umea, Sweden
Scand J Immunol; 15(1):136 1982

P3HR 1 is an EBV (Epstein-Barr Virus)-transformed Burkitt's lymphoma cell line, which has been shown to be IFN (interferon) sensitive. Upon IFN alpha addition the cell proceeds through the cell cycle and enters G0 after the first mitosis upon triggering by IFN. The rate of entry into G0 is dependent on the dose of IFN given. Dense cells differ in their cell cycle distribution compared to IFN-treated cells in that they seem to keep a normal cell cycle distribution as compared to exponentially growing cells. The levels of (2'-5') pA-synthetase was correlated to different growth states, and it was found that addition of (2'-5') pA core did not mimic the effect of IFN. (no Refs)

80. EFFECT OF 9-(2-HYDROXYETHOXYMETHYL)GUANINE ON VIRAL-SPECIFIC POLYPEPTIDE SYNTHESIS IN HUMAN CYTOMEGALOVIRUS-INFECTED CELLS.

Mar EC, Patel PC, Huang ES
Cancer Res. Center, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Am J Med; 73(1A):82-85 1982

Plaque-forming assay resulted in a 50% inhibitory dose by 9-(2-hydroxyethoxymethyl)guanine (acyclovir) against Towne strain human cytomegalovirus (HCMV) of approximately 98 umol. At the drug concentration of 200 umol, we did not detect any significant inhibition of viral DNA synthesis by cRNA-DNA hybridization. However, at this drug concentration, the synthesis of at least two viral-specific late polypeptides (150K and 67K) was significantly retarded up to 48 hr after infection, but resumed at 72 hr. These data suggest that acyclovir or its in vivo transformed derivative had a transient effect on viral-specific polypeptide synthesis in HCMV-infected human fibroblasts at a high drug concentration. (Author abstract) (19 Refs)

81. REPLICATION OF EPSTEIN-BARR VIRUS DNA IN LYMPHOBLASTOID CELLS TREATED FOR EXTENDED PERIODS WITH ACYCLOVIR.

Colby BM, Shaw JE, Datta AK, Pagano JS
Cancer Res. Center, Univ. North Carolina, Box 3, Swing Building, 217H, Chapel Hill, NC, 27514
Am J Med; 73(1A):77-81 1982

An Epstein-Barr virus (EBV)-producing human lymphoblastoid cell line (P3HR-1) was characterized after prolonged exposure to 9-(2-hydroxyethoxymethyl)guanine (acyclovir). P3HR-1 cells grown for 11 mo in the presence of acyclovir had the same number of EBV genomes (approx 15/cell) as did short-term acyclovir-treated cells. After removal of the drug, the number of EBV genome equivalents of long-term acyclovir-treated cultures (15/cell) returned to P3HR-1 control levels (340/cell). Indirect immunofluorescence studies demonstrated reduced percentages of long-term (6 to 12 mo) acyclovir-treated P3HR-1 cells expressing both EBV early antigens (EA) and viral capsid antigens (VCA). This contrasts with short-term acyclovir-treated cultures where EA is expressed at normal levels even though VCA expression is reduced. Restriction fragment patterns of the total EBV DNA from both short- and long-term acyclovir-treated cultures were identical with the exception of two fragments present in short- but not long-term acyclovir-treated cultures. EBV-associated DNA polymerase was present in long-term acyclovir-treated cultures with the level of activity, as determined by assay in vitro, comparable to that in untreated P3HR-1 cells. The polymerase activity in the treated cells was sensitive in vitro to acyclovir triphosphate, N-ethylmaleimide (NEM), and phosphonoacetic acid (PAA). These studies demonstrate that acyclovir inhibits the EBV-productive cycle in P3HR-1 cells continuously during extended periods of treatment. (Author abstract) (21 Refs)

82. EFFECT OF ACYCLOVIR ON HERPES SIMPLEX VIRUS REPLICATION IN A PERSISTENTLY INFECTED HUMAN LYMPHOBLASTOID CELL LINE (P3HR-1).

Shaw JE, Colby BM, Leong J, Bolling TJ
Univ. North Carolina, Box 3, Swing Building, 217H, Chapel Hill, NC, 27514
Am J Med; 73(1A):72-76 1982

We examined the effect of acyclovir on herpes simplex virus (HSV) replication in the persistently infected human lymphoblastoid cell line, P3HR-1. During 10 days of continuous exposure of P3HR-1 cells to 100 uM acyclovir there was a decrease in the number of cells expressing HSV antigens, the number of copies of HSV DNA per cell, and the infectivity of extracellular virus. A significant increase in each of these was detected after 14 days of continuous exposure of P3HR-1 cells to the drug, demonstrating that the replication of HSV has become resistant to inhibition by acyclovir. No apparent resistance of EBV replication to inhibition by acyclovir, however, was detected in HSV-infected P3HR-1 cells. The number of copies per cell of EBV and HSV DNA increased after exposure of HSV-infected P3HR-1 cells to the tumor promoter TPA (12-O-tetradecanoyl-phorbol-13-acetate). When cells were exposed continuously to acyclovir for 4 mo and then exposed to acyclovir and TPA simultaneously, the number of copies per cell of HSV DNA increased, but the number of copies per cell of EBV DNA increased by only a few, if any. The detection of P3HR-1 cultures of individual cells expressing both HSV and EBV antigens suggested that HSV and EBV productive cycles could occur simultaneously within the same cell. However, single cells very rarely expressed both antigens simultaneously. (Author abstract) (19 Refs)

83. DIFFERENT IN VITRO EFFECTS OF DUAL COMBINATIONS OF ANTI-HERPES SIMPLEX VIRUS COMPOUNDS.

Schinazi RF, Nahmias AJ
Dept. Pediatrics, Div. Infectious Diseases, Allergy and Immunology, Emory Univ. Sch. Medicine, 69 Butler St., S.E., Atlanta, GA, 30335
Am J Med; 73(1A):40-48 1982

Five promising antivirals have been tested individually and in pairs on herpes simplex virus (HSV) Types 1 (Strain F) and 2 (Strain G) in Vero cells. These are: 9-(2-hydroxyethoxymethyl)guanine (acyclovir, ACV), 9-beta-D-arabinofuranosyladenine (ara-A), 5-trifluorothymidine (TFT), E-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), and phosphonoformate (PFA). Various types of interactions depending on virus type were observed: synergistic [ara-A/TFT; ara-A/BVDU (G); BVDU/PFA (F)]; additive [ACV/ara-A; ACV/TFT; ACV/BVDU; ACV/PFA (G); BVDU/TFT; PFA/ara-A; PFA/TFT]; and sub-additive [ACV/PFA (F); ara-A/BVDU (F) and BVDU/PFA (G)]. Neither antagonism nor interference was noted for any combinations. (Author abstract) (35 Refs)

84. CHEMOTHERAPY ON HERPES VIRUS, PARTICULARLY THE EFFECT OF ANTIVIRAL AMINO ACID ANALOGUES.

Toyoshima S, Fukuma M, Fujita H, Seto Y
Div. Chemotherapy, Pharmaceutical Inst., Sch. Medicine, Keio Univ, Tokyo, Japan
Excerpta Med Int Congr Ser; 571:148-156 1982

The characteristics and antiviral effects of two selected amino acid analogs, N-naphthalenesulfonyl-DL-tryptophan (A-91) and N-ethyloxycarbonylaminomethyl-L-isoleucine (A-145), are presented. A-91 shows activity in various studies with herpes simplex virus (HSV) Type 1 and 2, and vaccinia virus in vitro and in vivo. A-91 and A-145 during a 1 hr absorption period did not affect the formation of plaques by HSV-1 and HSV-2 and did not inactivate viruses directly. The compounds do not induce interferon in mice. Results indicate both compounds inhibit viral multiplication but not at a very early stage. In female mice intravaginally infected with HSV-2, macroautoradiographic studies after iv administration of 14C-A-92 or 14C-A-145 showed high radioactivity in the genital organs with consequent prolongation of life span. Since HSV-2 is indicated as one of the possible causes of cervical cancer, these compounds may act as antitumor agents on cervical cancer. (5 Refs)

OTHER RELATED STUDIES

85. PLASMIN-ACTIVATED ANTI-CANCER PRODRUGS (MEETING ABSTRACT).

Weber MJ, Chakravarty PK, Johnson GL, Bruesch MR, Katzenellenbogen JA
University of Illinois, Urbana, IL
Conference on Cell Proliferation, Cancer and Cancer Therapy, February 17-19, 1982, New York, New York New York Academy of Sciences; :AP-24 1982

We have synthesized plasmin-activatable prodrug derivatives of acivicin, adriamycin, melphalan, and phenylenediamine mustard by coupling a specific tripeptide (D-Val-L-Leu-L-Lys) to an essential amino group of the parent drug. Because many tumors display elevated levels of plasminogen activator, we anticipate that high levels of plasmin will occur at the tumor site which will cause local activation of the prodrugs. We find that the prodrugs show as much as a twenty-fold improvement in selectivity for malignant cells in culture, compared to the parent drugs. As a prelude to in vivo testing of these prodrugs, we have examined a number of transplantable murine tumors for plasminogen activator activity. Of the tumors tested, B16 melanoma had the highest activity, which was 3-5 times higher than the most active of normal organs tested (brain and kidney). Moreover, mice carrying the B16 tumor displayed a marked elevation in the levels of fibrin degradation products in their serum. Thus, this tumor test system appears to be a suitable one for testing plasmin-activated prodrugs in vivo. (no Refs)

86. AFFINITY THERAPEUTICS. 1. SELECTIVE INCORPORATION OF 2-THIOURACIL DERIVATIVES IN MURINE MELANOMAS. CYTOSTATIC ACTIVITY OF 2-THIOURACIL AROTINOIDS, 2-THIOURACIL RETINOIDS, AROTINOIDS, AND RETINOIDS.

Watjen F, Buchardt O, Langvad E
Chemical Lab. II, H. C. Orsted Inst., Univ. Copenhagen, Universitetsparken 5, Copenhagen, Denmark
J Med Chem; 25(8):956-960 1982

The incorporation of 2-[35S]thiouracil and two of its derivatives into murine melanomas, in vivo, was studied. It was confirmed that 2-thiouracil has a marked affinity for melanin-producing tissue and that an affinity for such tissue could be sustained by 5-substituted 2-thiouracils. A series of derivatives of arotinoids and retinoids, with or without a 2-thiouracil group as a potential carrier to obtain affinity for melanomas, was examined for cytostatic activity, in vitro. None of these showed significant activity against murine melanomas. (Author abstract) (12 Refs)

87. CHEMOTHERAPY OF ADVANCED GASTRIC CANCER.

Weber W, Obrecht JP
Abteilung fur Onkologie, Departement fur Innere Medizin, Kantonsspital, CH-4031 Basel, Switzerland
Onkologie; 4(6):304-307 1981

Medical treatment of advanced carcinoma of the stomach in the past proved almost fruitless. Recent experience with cytotoxic drugs such as 5-fluorouracil, adriamycin, mitomycin C and nitrosoureas have begun to show evidence of definitive antineoplastic activity. Intensified efforts of studying new drugs and combinations are fully justified. (Author abstract) (21 Refs) (In GER)

88. RENAL TUBULAR TRANSPORT OF FOLIC ACID AND METHOTREXATE IN THE MONKEY.

Williams WM, Huang KC
Dept. Pharmacology and Toxicology, Univ. Louisville Health Sciences Center, Louisville, KY, 40292
Am J Physiol; 242(5):F484-F490 1982

Suspected proximal tubular location of the methotrexate (MTX) secretory system was studied in the monkey using standard clearance and stop-flow techniques and the renal handling of the folic acid was further characterized. Earlier observations that MTX undergoes net tubular secretion under conditions of free urinary flow were confirmed. In contrast, folic acid underwent net tubular reabsorption against a concentration gradient during free urinary flow. Secretion of both compounds was inhibited by p-aminohippuric acid and other organic acids but not by L-glutamic acid. (29 Refs)

89. RETINOIDS AS CHEMOPREVENTIVE AND ANTICANCER AGENTS IN INTACT ANIMALS (REVIEW).

Hill DL, Grubbs CJ
Southern Res. Inst., Box 3307-A, Birmingham, AL, 35255
Anticancer Res; 2(1/2):111-124 1982

Certain retinoids have prevented induction of cancer by carcinogens in the skin, mammary gland, and urinary bladder of experimental animals. In isolated experiments retinoids have also shown anticancer activity against esophageal, cervical, and hepatic cancers. No conclusive evidence of prophylactic activity against cancers of the lung or colon has been found. Retinoids have shown modest activity against those established cancers that are immunogenic. Retinoids apparently have antipromoting and general immunostimulative activities. (137 Refs)

90. THE MECHANISM OF RENAL CLEARANCE OF CISPLATIN (CIS-DICHLORODIAMMINE PLATINUM II) AND ITS MODIFICATION BY FUROSEMIDE AND PROBENECID.

Daley-Yates PT, McBrien DC
Biochemistry Dept., Brunel Univ., Uxbridge, Middlesex UB8 3PH, England
Biochem Pharmacol; 31(13):2243-2246 1982

When isolated rat kidneys are perfused with 30uM cisplatin there is net tubular transport of platinum, resulting in excretion of platinum at a rate 125% of the rate attributable to glomerular filtration alone. Probenecid and furosemide are drugs which have been reported to protect against cisplatin nephrotoxicity, by unknown mechanisms. When probenecid 0.3 mM is included in the perfusate net transport of platinum is increased to 200% of that accounted for by glomerular filtration alone. Increasing the concentration of probenecid to 3.0 mM does not significantly further increase the rate of excretion of platinum. The inclusion of furosemide 0.3 mM in the perfusate has no effect on the net tubular transport of platinum. However, at 3.0 mM furosemide causes a decrease in the net platinum transport and only 93% of platinum filtered at the glomerulus appears in the urine. Thin-layer chromatography revealed the presence of at least three platinum compounds in the urine in addition to cisplatin. We conclude that the renal excretion of cisplatin and its transformation products, even in this model system, is a complex process involving glomerular filtration, tubular excretion and tubular reabsorption. (Author abstract) (20 Refs)

91. CYTOSTATIC ACTIVITY AND METABOLIC EFFECT OF N-TRICHLOROMETHYLTHIO-4-CYCLOHEXANE-1,2-DICARBOXIMIDE ON EHRLICH ASCITES CARCINOMA CELLS.

Sturdik E, Drobnica L, Jamrichova S
Dept. Microbiology and Biochemistry, Slovak Technical Univ., 880 37 Bratislava, Czechoslovakia
Neoplasma; 29(2):205-214 1982

Effect of N-trichloromethylthio-4-cyclohexane-1,2-dicarboximide (NTCD) on energy-yielding and energy-requiring processes in Ehrlich ascites carcinoma (EAC) cells has been investigated. At concentrations higher than 10 ug/ml NTCD causes a rapid and practically full inhibition of both aerobic glucose uptake and lactate formation. On the other hand, at concentrations lower than 10 ug/ml, these metabolic parameters are stimulated. The stimulation of glycolysis, according to our previous results, suggests the interference of NTCD with mitochondrial functions. This image is supported by the marked inhibitory effect of NTCD on respiration of isolated mitochondria. The inhibition of glycolysis with higher concentrations of NTCD is the consequence of inactivation of hexokinase (EC 2.7.1.1), eventually of 6-phosphofructokinase (FC 2.7.1.11). The described effects of NTCD are given into coherence with chemical modification of appropriate functional SH groups of EAC cells by the compound studied. Proportionally to the dose and time NTCD inhibits the synthesis of macromolecules in whole EAC cells as measured by the incorporation of labeled adenine and valine into the TCA-insoluble fractions. The inhibition of biosynthetic processes followed is the consequence of exclusion of key processes in the energy metabolism and leads to the loss [illegible] EAC cells transplantability. (Author abstract) (28 Refs)

92. TUMOR AFFINITY AND DNA INTERACTIONS OF 57CO-BLEOMYCIN.

Kakinuma J, Honjo Y, Orii H
Tokyo Metropolitan Inst. Medical Sciences, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo 113, Japan
Radioisotopes; 31(4):175-178 1982

Tumor affinity of two isomeric forms of 57Co-bleomycin (BLM) was studied in Rous sarcoma-bearing SR-DDD-Br mice with respect to distribution of the Type I and Type II isomers in the tumor, blood, muscles, liver, and kidneys. DNA binding properties of the isomers were studied with the aid of DNA melting. Accumulation in the tumor tissues and stability of DNA binding of Type I isomer were higher than those of Type II. (5 Refs) (In JPN)

93. FACTORS MODIFYING THE ANTITUMOR EFFECT OF CHALONES FROM EHRLICH ASCITES CARCINOMA CELLS.

Kraskovskii GV, Mel'nov SB
Byelorussian Inst. Genetics and Cytology, Minsk, USSR
Dokl Akad Nauk BSSR; 26(6):562-564 1982

The effect of chalone from Ehrlich ascites carcinoma (EAC) on cell proliferation was studied in Af mice and in hyperdiploid line of EAC cells. In vitro incubation of tumor cells with EAC extract resulted in significant inhibition of EAC growth in mice. Transplantation of tumor cells without in vitro incubation with EAC extract did not inhibit proliferation of EAC cells in vivo. Administration of hydrocortisone prior to tumor transplantation produced inhibition of tumor growth. The most significant inhibition of tumor growth was observed in mice inoculated with hydrocortisone and transplanted with tumor cells that were preincubated with EAC extract in vitro. Incubation of target cells with trypsin enhanced the effect of chalone. These findings confirm the chalone activity of the extract of EAC cells. The most pronounced effect of chalone on proliferation of tumor cells was observed after in vitro incubation with target cells. (14 Refs) (In RUS)

94. MUTATIONS INDUCED BY GAMMA-RAYS AND FAST NEUTRONS IN CULTURED MAMMALIAN CELLS: DIFFERENCES IN DOSE RESPONSE AND RBE WITH METHOTREXATE- AND 6-THIOGUANINE-RESISTANT SYSTEMS.

Nakamura N, Suzuki S, Ito A, Okada S

Dept. Radiation Biophysics, Faculty Medicine, Univ. Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Mutat Res; 104(6):383-387 1982

The effects of fast neutrons on mutations induced by methotrexate (MTX) or 6-thioguanine (6-TG) were investigated in mouse lymphoma L5178Y cells. For MTX mutations, the dose-response curves were approx linear for both gamma-rays and neutrons and the relative biological effectiveness (RBE) was 1.3. For 6-TG mutations, the dose-response curve for gamma-rays were upward concave while that for neutrons was almost linear; the RBE values were dose dependent and increased from 2.4 at higher doses to greater than 5 at lower doses. (13 Refs)

95. IN VITRO ASSAY OF THE EFFECTS OF PSORALENS PLUS ULTRAVIOLET RADIATION ON HUMAN LYMPHOID CELLS.

Kraemer KH

NIH, Building 37, Room 3E24, Bethesda, MD, 20205

JNCI; 69(1):219-227 1982

An in vitro assay system that mimics some of the features of in vivo oral methoxsalen photochemotherapy (PUVA) in relation to human lymphoid cells was developed. In this assay, suspension cultures of human lymphoid cells were subjected to therapeutic concentrations of 8-MOP and to a UVA radiation spectrum modified to approximate the dermal exposure. The assay permitted correlation and quantitation of multiple 8-MOP plus UVA-induced biological and physical alterations in the same assay system. Thus were demonstrated inhibition of DNA synthesis, reduction of cell survival, production of DNA cross-links, and loss of mixed leukocyte reactivity induced by combinations of 8-MOP and UVA in or near the presumed therapeutic range. This assay may be useful for predicting lymphoid cellular toxicity of other photoactive agents as well as for examining the molecular effects of these agents. (Author abstract) (51 Refs)

96. COMPARATIVE PHOTOBIOLOGY OF PSORALENS.

Ashwood-Smith MJ, Natarajan AT, Poulton GA

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JNCI; 69(1):189-197 1982

The comparative photobiological effects of several fucocoumarins [ie, angelicin, psoralen, 8-methoxypsoralen (8-MOP), and 5-methoxypsoralen (5-MDP)] have been evaluated in a number of biological systems. The photosensitized induced lethality and genetic damage have been assessed in bacterial, animal, and human cells, and the rank order of effectiveness established psoralen as the most active compound followed by 8-MOP, 5-MOP, and angelicin. 5-MOP and 8-MOP are, however, essentially equally active in the production of chromosome damage in human cells in vitro. (Author abstract) (15 Refs)

97. EFFECT OF ANTHRACYCLINE ANALOGUES ON THE APPEARANCE OF NEWLY SYNTHESIZED TOTAL RNA AND MESSENGER RNA IN THE CYTOPLASM OF ERYTHROLEUKEMIA CELLS.

Long BH, Willis CE, Prestayko AW, Crooke ST

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Mol Pharmacol; 22(1):152-157 1982

Effects of the structural analogs adriamycin (ADM), daunomycin (DNM), carminomycin (CMM), 4-demethoxydaunomycin (4D-DNM), pyrromycin (PYM), marcellomycin (MCM), and aclacinomycin (ACM) upon total RNA synthesis and appearance of total RNA and polyadenylated (poly(A)+)-RNA in the cytoplasm of uninduced Friend erythroleukemia cells were studied. Each drug was tested at six different concentrations and compared with the av of two controls in three separate experiments. Generally, there were greater differences between the effects of different drugs than were exhibited by the same drug upon the different RNA populations. The differences were clearer when expressed as median dose (IC50) values. The Class II anthracyclines, MCM and ACM, inhibited RNA synthesis by 50% at 60 nanoM, which is 20-50 fold lower than the IC50 value for class I anthracyclines, DNM and ADM. Inhibition of the appearance of poly(A)+-RNA in the cytoplasm closely paralleled inhibition of total RNA synthesis for ADM, DNM, and CMM, whereas the appearance of poly(A)+-RNA was less sensitive to inhibition by the Class II drugs. IC50 values for inhibition of the appearance of total RNA into the cytoplasm were consistently 1/2 to 1/3 the respective IC50 values for total cellular RNA synthesis inhibition, suggesting that one possible factor in the effects of these anthracyclines is alteration of post-transcriptional events. Pre-messenger RNA and pre-ribosomal RNA effects probably play a minor role in inhibiting the appearance of RNA in the cytoplasm compared to the activity at the transcriptional level. (30 Refs)

98. ACTIONS OF CIS-DIAMMINEDICHLOROPLATINUM ON CELL SURFACE NUCLEIC ACIDS IN CANCER CELLS AS DETERMINED BY CELL ELECTROPHORESIS TECHNIQUES.

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Cancer Res; 42(9):3565-3573 1982

Whole-cell electrophoresis determinations were made on a variety of tumor cell suspensions in order to examine the charged groups on the cell surfaces. We report here evidence which indicates the presence of nucleic acids on the surfaces of the tumor cells. Cells of the ascitic and solid forms of the Sarcoma 180 mouse tumor, grown in ICR mice, showed a decrease of 10 to 20% in electrophoretic mobility when incubated with nucleases. One variant, S-180, exhibited sensitivity to RNase only; another variant was sensitive to both RNase and DNase, while different tumor lines were shown to be sensitive to DNase only. Treatment of tumor-bearing animals with a therapeutic dose of cisplatin resulted in a loss of tumor cell mobility identical to that produced by the nuclease incubations of the control cells. Incubation of the cisplatin-treated tumor cells with nucleases produced no change in mobility. The isoelectric points of these cells are consistent with the loss of a group with a low pK value in both cisplatin-treated cells and nuclease-incubated cells. Using the S-180 tumor sensitive to both RNase and DNase, the rates of the two enzymes were additive, but the mobility decreased to the same level regardless of whether the enzymes were used alone or together. This suggests that both enzymes act on the same site. RNase and DNase immobilized on agarose beads were capable of lowering the mobility of the cells upon incubation, confirming the surface location of these nucleic acid residues. S-180 tumor cells were also placed in a tissue culture medium at 37 C for up to 22 hr and were treated in vitro with cisplatin and other metabolic inhibitors. Nucleic acid or protein synthesis inhibitors produced a loss of the cell surface nucleic acids. In another in vitro experiment, the nucleic acids were first removed by nucleases, and, when the cells were incubated at 37 C, the nucleic acids reappeared. Disappearance with the inhibitors or reappearance after digestion exhibited a half-time of about 2 hr. Surface nucleic acids were detected by this electrophoresis technique on all of several types of tumor cells but not on any normal cells examined. (18 Refs)

99. MOLECULAR ASSOCIATION BETWEEN DOXORUBICIN (ADRIAMYCIN) AND DNA-DERIVED BASES, NUCLEOSIDES, NUCLEOTIDES, OTHER AROMATIC COMPOUNDS, AND PROTEINS IN AQUEOUS SOLUTION.

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Mol Pharmacol; 22(1):158-165 1982

The ability of doxorubicin (DRN) to form complexes was demonstrated in a nonbiological system by measuring the partition coefficient in a medium of 1-octanol and 0.05 M Tris-distilled water soln and in a biological system by measuring the transmembranous DNR transport and distribution at equilibrium in a medium of human red blood cells and their suspending fluid. Addition of various DNA-derived bases, nucleosides, and nucleotides decreased the partition coefficient of DRN in the nonbiological system, indicating increased hydrophilicity, or decrease of activity in the aqueous phase. Purine derivatives had greater influence than pyrimidine derivatives. The partition coefficient was not affected by temperature (21-60 C) at low DRN concentration in the absence of added compounds; ATP increased the effect of temperature in a concentration-dependent way. The various compounds affected the initial cellular DRN net uptake and equilibrium distribution in red blood cells. ATP decreased both values, and had a more pronounced effect when salt soln was the suspending medium than when cells were in autologous plasma. The activity coefficient of DRN in plasma was 0.15 relative to that in salt soln when activity coefficient was calculated from the apparent permeability coefficient. (30 Refs)

100. THE MODIFICATION OF GLYCOPROTEIN BIOSYNTHESIS AS A POTENTIAL BASIS FOR CANCER CHEMOTHERAPY.

Morin MJ
State University of New York at Buffalo, Buffalo, NY
Diss Abstr Int [B]; 42(9):3625-B 1982

The biochemical and therapeutic effects of the sugar analogue 6-deoxy-6-fluoro-D-galactose (6-F gal) and the antibiotic tunicamycin (TM) were examined to establish the extent to which modification in glycoprotein synthesis were required for the expression of potentially useful alterations in tumor cell characteristics. Exposure of L1210 leukemic cells to nongrowth inhibitory doses of 6-F gal apparently induced only subtle modifications in glycoproteins, the most prominent of which was a dose-dependent and time-dependent decrease in the activity of cell surface sialyltransferase. Exposure of L1210 leukemic cells to TM, which inhibited the first step in the synthesis of asparagine-linked glycoproteins, resulted in less subtle modifications in tumor cell behavior. Specific alterations in plasma membrane components and in tumor cell ultrastructure, including distentions in the endoplasmic reticulum and nuclear membrane, were apparent in cells treated with doses of the antibiotic at which glycosylation processes were selectively inhibited. Examination of the effects of the exposure of L1210 ascites to TM in vitro on the subsequent transplantability of these cells in vivo revealed a dose-dependent increase in the survival of normal mice without a significant decrease in the tumorigenicity of the same cells implanted into immunologically compromised mice. The demonstration of resistance to further challenge with a lethal inoculum of tumor cells among mice which survived the initial exposure to TM-treated cells gave further evidence of an immunological component to the dose-dependent increase in host survival. Attempts to invoke a similar response in tumor-bearing mice with a direct administration of TM were limited by the predominant hepatotoxicity of the antibiotic. The toxicity of TM in mice could be diminished with a prior infusion of D-mannose and a combination of the two resulted in enhanced inhibition of L1210 leukemic cell growth in vitro and gave some evidence of a minor increase in the survival times of tumor bearing mice. (no Refs)

101. THE ACTION OF SPIN LABELED CIS-PLATINUM DERIVATIVES IN ESCHERICHIA COLI.

Riley MI
University of Kansas, Lawrence, KS
Diss Abstr Int [B]; 42(7):2668- 1982

Cis-dichlorodiammine platinum, cis-DDP, and many of its derivatives have antitumor activity. The cytotoxic action of these platinum compounds is thought to involve complexes they form with DNA. However, the molecular nature and biological significance of these lesions remain unclear. Such information is difficult to obtain due to the lack of convenient biochemical probes. These studies utilized newly synthesized spin labeled derivatives of cis-platinum (II), PDN-1, and cis-platinum (IV), PDDN-5, to acquire new information regarding the molecular nature of platinum binding in bacteria and as tracers in related chromatography studies. Such information was correlated with its toxic effects and radiosensitizing ability. The results are summarized below. PDN-1 is better killing agent that PDDN-5, while both these spin labeled platinum derivatives are less potent than the parent drug, cis-DDP. Interestingly, both derivatives are less toxic in the absence of oxygen. The general shape of toxicity curves, comprised of a shoulder region and followed by an exponentially dependent region, suggests that these compounds are radiomimetic agents. Both spin labeled compounds are good hypoxic radiosensitizers at concentrations where they become mildly toxic, while they have minimal effect on radiation response in the presence of oxygen. PDDN-5 was able to perturb the radiation survival kinetics to a greater extent than PDN-1. The presence of the bound platinum component during irradiation may represent a new class of radiosensitizers, as revealed by the survival data from various drug-irradiation sequences. (no Refs)

102. ACCUMULATION AND RELEASE OF VINBLASTINE AND VINCRISTINE BY HELA CELLS: LIGHT MICROSCOPIC, CINEMATOGRAPHIC, AND BIOCHEMICAL STUDY.

Lengsfeld AM, Dietrich J, Schultze-Maurer B
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Cancer Res; 42(9):3798-3805 1982

The effect of vinblastine (VLB) and vincristine (VCR) on the survival and proliferation of HeLa cells has been studied during continuous and after 3-hr-incubations using cell counting and time lapse cinematography. VLB and VCR are accumulated in the cells during drug exposures as shown with 3H-labeled drugs. The intracellular drug concentration after a 3-hr-incubation with therapeutic doses (VLB, 0.1 ug/ml, or VCR, 0.03 ug/ml) and thorough drug removal is 150 to 500x higher than that in the incubation medium. Both drugs are released from the cells upon restoration to alkaloid-free medium reaching concentrations that are lethal to the cells during continuous incubation. There is however, a difference in the release of the two drugs. VLB is quickly and readily released from the cells while the release of VCR occurs slowly, since VCR is tenaciously retained by the cells. Both drugs are released predominantly from living cells. (Author abstract) (11 Refs)

103. DNA DAMAGE AND SELECTIVE TOXICITY OF DOPA AND ASCORBATE: COPPER IN HUMAN MELANOMA CELLS.

Parsons PG, Morrison LE
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Cancer Res; 42(9):3783-3788 1982

Six of eight human melanoma lines showed increased sensitivity to killing by dopa and by ascorbate:copper compared with two fibroblast strains and four other human cell lines of nonmelanoma origin. Catechol, epinephrine, and alpha-methyldopa, but not 5,6-dihydroxyindole, exhibited a similar degree of selectivity. Toxicity was greatly reduced when brief exposure times or high cell densities were used. Depending upon culture conditions, melanoma cells accumulated more [3H]dopa- and [14C]ascorbate-derived isotopic label within the first 5 min than fibroblasts, but after 1 hr this difference was less marked. The catalase activity in melanoma cells was not less than that in fibroblasts. Using two independent methods to determine each type of damage, dopa and ascorbate:copper were found to induce DNA breaks in both cell types but not DNA repair synthesis or DNA interstrand cross-links. More DNA breaks were found in melanoma cells (two lines) than in fibroblasts. Semiconservative DNA synthesis was inhibited immediately, recovered within 6 hr, and in melanoma cells was again inhibited after 24 hr. RNA synthesis was inhibited less than DNA synthesis. Human cell lines with differential sensitivity to alpha-radiation, ultraviolet light, cross-linking agents, or monofunctional alkylating agents exhibited normal survival levels when treated with dopa or ascorbate:copper. (Author abstract) (36 Refs)

104. STUDIES IN NONSTEROIDAL ANTIESTROGENS AND RECEPTOR MEDIATED CYTOTOXICITY.

Robertson DW
University of Illinois at Urbana-Champaign, Urbana, IL
Diss Abstr Int [B]; 42(9):3694-B 1982

The nonsteroidal antiestrogens Z-tamoxifen and Z-hydroxytamoxifen and their E isomers have been prepared in high specific activity tritium-labelled form. This permitted a comparative study of the metabolism and pharmacokinetics of Z-tamoxifen, an antiestrogen, and E-tamoxifen, an estrogen. It was found that different metabolites accumulate in the rat uterus following treatment with E- and Z-tamoxifen; this may account for their different endocrinological properties. The metabolism of the antiestrogens U-23, 469 and CI-628 has also been studied using radio-labelled materials and the identity of their biologically-important metabolites confirmed chemically and chromatographically. A series of compounds designed to probe the importance of side-chain basicity in antiestrogens has been prepared, as has a series to elucidate the structural determinants necessary for evoking antiestrogen action; preliminary biological experiments with the compounds are reported. Several chemically-reactive tamoxifen analogs have been synthesized and evaluated biochemically and biologically as potential cytotoxic agents for tumors containing estrogen receptors. An aziridine analog of tamoxifen, tamiridine, is a binding site-specific and extremely potent irreversible inactivator of the estrogen receptor from lamb and rat uteri and MCF-7 human breast cancer cells. The inactivation is rapid and efficient with 1 nM tamiridine resulting by three hours in the inactivation of 0.2-0.9 nM of receptor. (no Refs)

105. TUMORICIDAL EFFECT OF MACROPHAGES EXPOSED TO ADRIAMYCIN IN VIVO OR IN VITRO.

Martin F, Caignard A, Olsson O, Jeannin JF, Leclerc A
Res. Group Digestive Tumors, Lab. Immunology, Institut National de la Sante et de la Recherche Medicale, 21033 Dijon, France
Cancer Res; 42(9):3851-3857 1982

Peritoneal macrophages from BD IX rats collected 24 hr after an ip injection of Adriamycin (10 mg/kg) were cytotoxic to syngeneic cancer cells in culture. In contrast, incubation in vitro in Adriamycin solutions did not evoke tumoricidal activity in peritoneal macrophages, whatever the incubation time (from 1 to 24 hr) and the Adriamycin concentration (from 1 ng to 100 ug/ml). Macrophages incubated with Adriamycin in vitro accumulated the drug in their nuclei, whereas macrophages from animals receiving Adriamycin in vivo accumulated it in cytoplasmic vacuoles. Early observation of peritoneal cells after in vivo exposure to Adriamycin shows that Adriamycin is concentrated in mast cell granules which are released and then phagocytosed by peritoneal macrophages. Mast cells exposed to Adriamycin in vitro can induce macrophages to become cytotoxic. These facts explain the difference between macrophages exposed to Adriamycin in vivo and in vitro. Adriamycin fluorescence appears in nuclei of cancer cells incubated with in vivo-labeled macrophages, suggesting that macrophages can directly transfer the drug into cancer cells and therefore play a role in the Adriamycin antitumor effect. (Author abstract) (22 Refs)

106. EFFECTS OF ADRENAL CORTICAL STEROIDS AND OSMOTIC BLOOD-BRAIN BARRIER OPENING ON METHOTREXATE DELIVERY TO GLIOMAS IN THE RODENT: THE FACTOR OF THE BLOOD-BRAIN BARRIER.

Neuwelt EA, Barnett PA, Bigner DD, Frenkel EP
Dept. Surgery (Div. Neurosurgery), Biochemistry, Oregon Health Sciences Univ., Veterans Admin. Medical Center, Portland, OR, 97201
Proc Natl Acad Sci USA; 79(14,part1):4420-4423 1982

The effect of adrenal cortical steroids and osmotic blood-brain barrier modification on methotrexate delivery to normal and glioma-bearing rats was studied. In animals with the avian sarcoma virus-induced glioma, osmotic blood-brain barrier modification resulted in significantly increased delivery of methotrexate to the tumor-bearing hemisphere (including the tumor, the brain around the tumor, and the brain distant to the tumor), compared to the nonmodified hemisphere or to control animals. The administration of adrenal steroids, followed by intracarotid methotrexate, resulted in slightly decreased chemotherapeutic agent (methotrexate) delivery to the tumor, the brain around the tumor, and the brain distant to the tumor. When adrenal steroids were given prior to barrier modification and methotrexate therapy, the level of methotrexate was significantly less in the tumor. These studies provide evidence that the blood-brain barrier exists in tumors and is a factor in drug delivery to tumors. Steroid administration greatly interferes with the enhancement of drug delivery to tumors that can be achieved with osmotic blood-brain barrier modification. (Author abstract) (17 Refs)

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